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Principles of Drug Therapy in Neurology (2 ed.)

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Fundamentals of Drug Therapy in Neurology

Chapter: Fundamentals of Drug Therapy in Neurology
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The number of drugs available for treatment of neurological disorders continues to expand steadily and the aim of this book is to provide a perspective for neurologists, psychiatrists, and other clinicians on how they can be used effectively. This perspective includes information about the pathophysiology of disease as well as drug interactions with the nervous system and the rest of the body. This introductory chapter deals with the fundamental concepts that are common to more specific treatment issues covered in detail in the rest of the book (Table 1–1). First we discuss some major molecular targets of drug action in the nervous system, an area that has expanded greatly as a result of the use of molecular genetic and electrophysiological techniques. The interaction of drugs with these targets is generally known as pharmacodynamics (PD) or the study of mechanisms of action and the relationship between drug concentration and effect. Then we discuss the absorption, distribution, metabolism and elimination of drugs, which determine their pharmacokinetics (PK). Taken together, a drug's PD and PK characteristics define its therapeutic window or the range of dose and/ or blood level at which it has optimal effect with minimal side effects. For many drugs these characteristics are under genetic control and this is the major focus of the field of *pharmacogenetics*. Genetic variation in the distribution and metabolism of drugs as well as in targets of drug action such as ion channels and neurotransmitter receptors are being recognized at an increasing rate. Pharmacogenetic factors can influence the dose of a drug required for treatment of individual patients, as well as its efficacy if a mutation is present in its molecular target of action. Another important factor that strongly influences drug therapy in neurology is the *toxicity* of these drugs. Because they target the nervous system, these drugs are prone to produce potentially disabling effects on cognition and other brain functions and this often influences the choice of drugs for individual patients. Finally we discuss the *influence of age* on effects of nervous system drugs, especially on fetuses, pregnant women, and elderly individuals.

Table 1–1 Determinants of Drug Therapy for Neurologic Disorders
Molecular targets, pharmacodynamics
Absorption, distribution, metabolism, and elimination
Blood brain barrier
Pharmacogenetics
Toxicity or adverse effects
Age of patient



Molecular targets of drug action in the nervous system

Excitatory and Inhibitory Synapses

Synapses are major targets of drug action in the nervous system and many molecules associated with synapses, including neurotransmitter receptors, voltage-dependent ion channels, transporters, and enzymes, have been characterized at the molecular level.[1] Chemical synapses between neurons are the primary sites where interneuronal communication and information transfer in the nervous system can be modulated.[2] Although numerous molecules have neurotransmitter properties, the so-called classical neurotransmitters including glutamate, GABA (γ-aminobutyric acid), dopamine, norepinephrine (NE), serotonin, and acetylcholine predominate in terms of pharmacotherapy in neurology, while others such as neuropeptides are also involved in neuroendocrine function and pain. A single neuron may contain and release more than one transmitter, such as acetylcholine and a peptide (somatostatin) or GABA and a peptide. Purely electrical synapses are also present in the nervous system, but drug action at these sites has not been described. The majority of synapses are excitatory and use the amino acid glutamate as their neurotransmitter.[3] It has been estimated that more than 70% of neurons release the excitatory amino acid glutamate when excited.[4] Glutamate synapses are ubiquitous throughout the brain and mediate learning and memory, motor and sensory processing, and vision and hearing.[5],[6] Disorders of glutamate synaptic function have been implicated in nearly every major neurological disease including epilepsy, movement disorders, stroke, dementia, and other neurodegenerative diseases.[7],[8] About one third of synapses in the nervous system are inhibitory and use GABA as their neurotransmitter. Disorders of GABA synaptic function have been identified in several disorders and especially in epilepsy, and numerous sedative and anticonvulsant drugs act at GABAergic synapses.[7],[9]

The biochemical machinery associated with glutamate synapses is shown in Figure **1–1** and illustrates some features common to most synapses. Neurotransmitters are synthesized and stored in presynaptic vesicles and released from depolarized nerve terminals. They bind specifically to presynaptic or postsynaptic receptors, which recognize the neurotransmitters chemical conformation. In the case of glutamate, which is a small flexible amino acid, three different types of postsynaptic receptors, can recognize one of its unique conformations. AMPA receptors (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid), also referred to as AMPA/kainite receptors, are ligand-gated ion channels that mediate most of the fast excitatory activity in the brain and are involved in learning and memory and epilepsy.[10,11] Ligand-gated ion channels are also referred to as ionotropic receptors to distinguish them from metabotropic receptors that are linked to enzymes that control the formation of second messenger molecules (Figure **1–2**). The anticonvulsant topiramate is an antagonist at these AMPA receptors.[1] They are made up of four subunits selected from four different types designated GluR1–4. Most AMPA receptors are either tetramers of Glur1 or GluR4, or composed of two GluR2 subunits and either GluR1 or GluR3 subunits (Figure **1–3**). Those AMPA receptors that contain GluR2 will be impermeable to calcium while those without it will flux calcium, potentially making neurons more vulnerable to injury.[10]

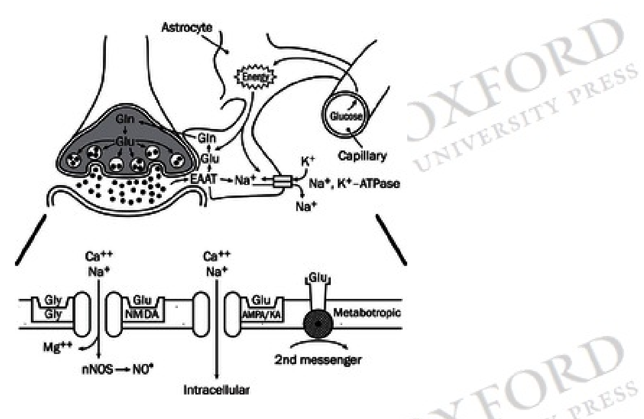


Figure 1–1.
The glutamatergic synapse and the glutamate (Glu)/glutamine (Gln) cycle.

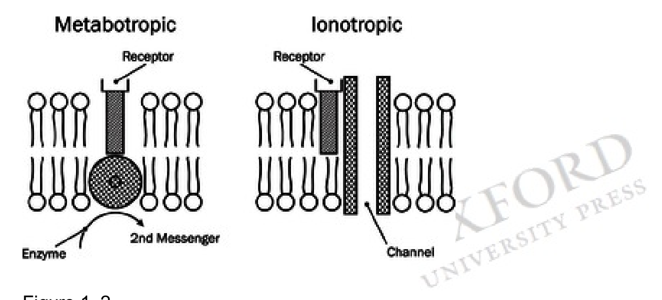




Figure 1–2.
Glutamate receptor types.



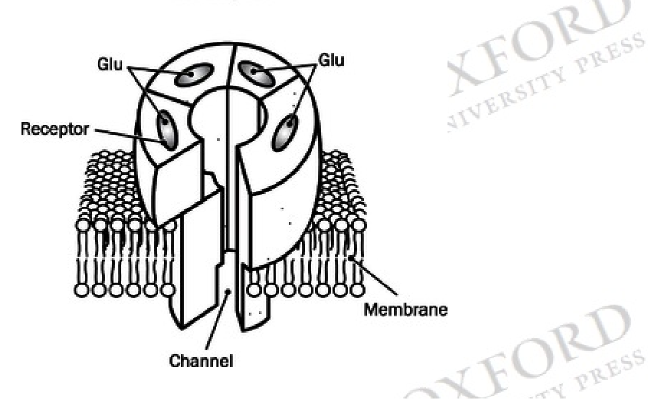






Figure 1–3.
AMPA glutamate receptor.

Next to AMPA receptors in the synaptic membrane are N-methyl-D-aspartate (NMDA)-type glutamate receptors, which are only opened when there is enough AMPA receptor activity to depolarize the membrane and release magnesium, which normally occupies the pore of the NMDA channel.[5] These receptors are also tetramers (2 NR1 and 2 NR2 subunits) and have a special role in neuronal plasticity and memory formation.[12] Another special feature of NMDA receptors is the requirement that the amino acid glycine (Gly) must also occupy a receptor site to open the NMDA channel. Drugs that block NMDA receptors include dextromethorphan, a cough suppressant; felbamate, which is approved for treatment of epilepsy; and memantine, which is approved for treatment of dementia.[8] Dextromethorphan, a competitive NMDA anatagonist, has also been combined with quinidine to treat pseudobulbar affect.[13] Metabotropic glutamate receptors are a third type located in glutamate synapses and they are linked to G proteins that stimulate phosphoinositide metabolism or reduce adenosine 3′-5′ cyclic monophosphate or cyclic AMP (cAMP) production.[1] Activation of the second messenger systems regulated by cAMP and phospholipase C (phosphoinositide turnover) appears to produce mutual interactions and competing actions at the cellular level. Often these discrete systems are organized in a regionally complementary fashion. Metabotropic glutamate receptors have roles in plasticity and influence the activity and trafficking of AMPA and NMDA receptors.[14,15] The diversity of receptors for glutamate at excitatory synapses allows for complex physiological modulation of brain excitability as well as drug therapies.

Like receptors for glutamate, inhibitory GABA receptors are diverse based on their subunit composition (Figure **1–4**).[16,17] GABA-A receptors are fast response ligand-gated chloride channels that inhibit neuronal activity by driving chloride inward causing hyperpolarization. Benzodiazepines and numerous anticonvulsants inhibit neuronal firing by activating GABA-A receptors. These receptors are related to nicotinic acetylcholine receptors, glycine receptors, and some serotonin receptors, and they are composed of five subunits selected from α, β, δ, and Y types of subunits.[9] GABA-B receptors also have an important role in the nervous system to inhibit presynaptic release of neurotransmitters including glutamate.[18] In contrast to the GABA-A receptors, these receptors are not linked to ion channels but are metabotropic G-protein-linked receptors. Baclofen reduces spasticity in part by activating GABA-B receptors that inhibit release of glutamate from presynaptic dorsal root axons in the spinal cord.[19]

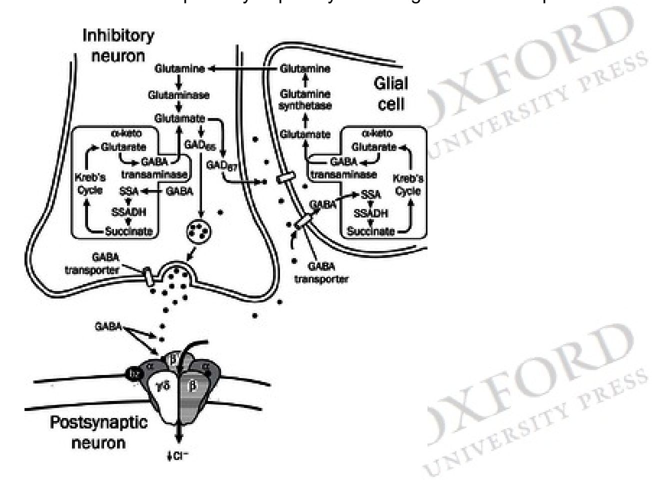




Figure 1–4.
GABAergic synapse and synthesis of GABA from glutamate.

The release of glutamate and GABA from presynaptic terminals into the synaptic cleft is tightly coupled to their removal by an energy dependent process (Figures **1–1** and **1–4**). All of the classical neurotransmitters are removed quickly from the synaptic cleft after release from the nerve terminal in order to limit their duration of action. In the case of glutamate and GABA, transporters on glia that surround the synapses perform this function, and energy for the pump is supplied by a sodium gradient created by Na+,K+-ATPase.[4] Adenosine triphosphate (ATP) for this reaction is in turn supplied by anaerobic metabolism of glucose delivered to the astroglia. Glutamate removed by the excitatory amino acid transporter (EAAT) is converted to glutamine (Gln) within the astroglia and then moves into nerve terminals where it is converted to glutamate by glutaminase. GABA is also involved in this cycle because it is also taken up into nerve terminals and converted to glutamate through α-ketoglutarate and then to GABA by glutamate decarboxylase (GAD) at inhibitory synapses (Figure **1–4**). The glutamate-glutamine cycle is coupled to glucose consumption in the brain and accounts for a major fraction of glucose consumption observed in functional imaging studies with glucose positron emission tomography (PET).[4,20] This suggests that a major share of the PET signal associated with brain activity is related to release and re-uptake of glutamate and GABA at neuronal synapses.

Voltage-Gated Ion Channels

Although receptors for glutamate and GABA require activation by neurotransmitters, many important ion channels do not require neurotransmitters to open them but open in response to depolarization of neuronal membranes. These voltage-gated ion channels comprise a family of more than 100 genes and they include some of the most important targets for action of anticonvulsants and some other drugs.[21] Voltage-gated sodium channels are responsible for sustained repetitive neuronal firing in models of epilepsy, and they are important targets for anticonvulsants such as phenytoin, carbamazepine, and lamotrigine (Figure **1–5**)A[22] Numerous mutations linked to genetic epilepsy syndromes have been found in genes for these channels.[23] For example, mutations in the SNC1A gene for the $Na_v1.1$ neuronal sodium channel α-subunit have been found in families with generalized epilepsy with febrile seizures plus (types 1 and 2) and in children with severe myoclonic epilepsy of infancy (SMEI, Dravet syndrome).[24–26] Voltage-gated channels for calcium, potassium, and chloride are also important targets for antiepileptic drugs as well as drugs for other disorders such as spasticity (Chapters 3 and 9).[1,22]

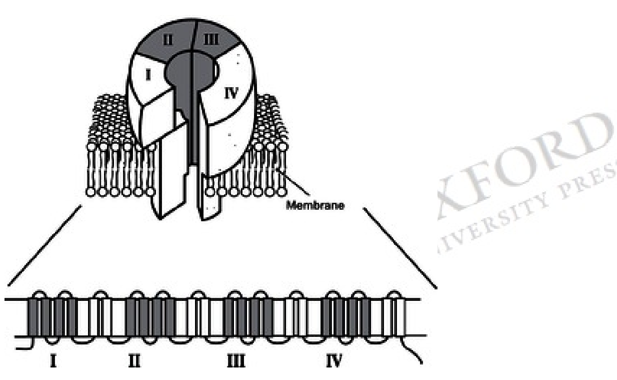




Figure 1–5.
Voltage-gated sodium channel.dopamine are energy dependent and relatively substrate specific.

Catecholamine Synapses

Synapses that use the catecholamines dopamine and NE as transmitters are important targets for therapy for movement disorders, as well as cognitive and behavioral disorders.[27] Major pathways that use these transmitters include the mesolimbic and striatonigral dopamine projections and the NE projection from the pons to the cerebral cortex. Figure **1–6** shows a diagram of the synaptic machinery for a dopamine synapse, which is an important target for therapy in Parkinson's disease, other movement disorders, psychiatric disorders, and addiction disorders (Chapters 2, 13, and 18). The processes involved in brain NE synapses are very similar to those in dopamine neurons except that these neurons also contain the enzyme dopamine ß-hydroxylase, which converts dopamine to NE. For treatment of patients with Parkinson's disease, the precursor amino acid L-dopa, is typically administered with carbidopa, which inhibits Lamino acid decarboxylase in the periphery but cannot cross the blood brain barrier (BBB). This markedly reduces the dose needed to elevate L-dopa in the central nervous system and prevents systemic side effects such as nausea, vomiting, and hypotension. L-dopa can cross the BBB and is decarboxylated within the synapse by L-amino acid decarboxylase (L-AADC) to form dopamine in residual nerve terminals and possibly also in the striatal extraneuronal space. Tyrosine hydroxylase is the rate-limiting step in synthesis so that raising the supply of L-dopa elevates available dopamine in the synapse. Dopamine (DA) is concentrated in vesicles by vesicular monoamine transporters (VMAT) and then released into the synaptic cleft.[28] Amantadine, an antiviral drug sometimes helpful for Parkinsonism, may act by increasing release of dopamine. Actions of neurotransmitters in the synaptic cleft are terminated either by re-uptake into the nerve terminal by trasporters or by enzymatic degradation by monoamine oxidases (MAO) and catechol-O-methyl transferase (COMT) and diffusion away from the synaptic cleft. As for glutamate and GABA, re-uptake processes for dopamine are energy dependent and relatively substrate specific.

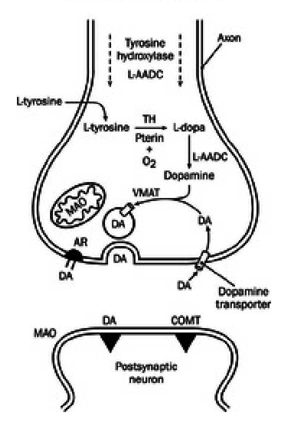




Figure 1–6.
Dopamine synapse.

Drugs such as cocaine, amphetamine, tetrabenazine, and reserpine can block re-uptake of dopamine and thereby influence the amount of neurotransmitter that is available in the synapse.[29] Initially, neurotransmitter accumulates in the synaptic cleft, causing acute agonist effects, but with chronic administration depletion of transmitter vesicles can occur. For example, reserpine blocks re-uptake at both catecholamine and serotonin nerve terminals by vesicular transporters, causing depletion of neurotransmitters, and some patients develop depression as a side effect.[30,31] Both reserpine and tetrabenazine are useful for treating hyperkinetic movement disorders (Chapter 2). Drugs differ with respect to their selectively as monoamine re-uptake inhibitors. The older tricyclic antidepressants such as amytriptyline, desipramine, and nortriptyline inhibit re-uptake of both NE and serotonin (Chapter 13). Methylphenidate used for attention deficit hyperactivity disorder (ADHD) is a relatively selective blocker of synaptic uptake of dopamine but does not stimulate indiscriminate release of vesicular stores like amphetamine does.[27] This may contribute to the low risk of developing dependency on this drug. Another stimulant used for ADHD is atomoxatine, which selectively blocks uptake of NE.[32] Clonidine also acts selectively on NE neurons by stimulating α-2 adrenergic autoreceptors that reduce their activity.

Monoamine oxidases (MAOs) are a group of enzymes that inactivate catecholamines and serotonin by oxidative deamination, and treatment with MAO inhibitors results in marked increases in brain concentrations of NE, serotonin, and dopamine (Chapter 13). These neurotransmitters accumulate both within the nerve terminals and secondarily in the synapses. MAO inhibitors were widely used in the past for depression. A major risk of treatment, which results from peripheral actions of MAO inhibitors, is abrupt development of hypertension.[33] This adverse reaction occurs after ingestion of foods containing tyramine, a catecholamine agonist, which may accumulate at peripheral sympathetic synapses. Selegine, a selective MAO inhibitor that reduces activity of MAO type B, can improve motor function in some patients with early Parkinson's disease by increasing available dopamine.[34] Inhibitors of COMT, a degradative enzyme present in the synapse, can also improve motor function in these patients.[35] Mutations in the gene for COMT have been linked to psychiatric and cognitive disorders.[36]

The postsynaptic effects of dopamine are mediated by two receptor families: D-1/D-5 receptors, which are excitatory and positively coupled to adenylyl cycles, and D-2/D-4

receptors, which are inhibitory and negatively coupled to adenylyl cyclase.[27] D-1 receptors are enriched in the frontal lobes and are involved in learning, memory, and attention.[37] However, D-2 receptors are more numerous than D-1 receptors in the brain, and blockade of D-2 receptors is thought to be responsible for the beneficial effects of all the major antipsychotic medications. Stimulation of D-2 receptors also mediates the beneficial effects of L-dopa and dopamine agonists in patients with Parkinson's disease. The importance of D-2 receptors as targets of therapy in both psychiatric and movement disorders accounts for the occurrence of Parkinsonian side effects in patients treated with neuroleptics and psychiatric side effects in patients treated with L-dopa and dopamine agonists. Second-generation antipsychotics including risperidone, olanzapine, quetiapine, and ziprasidone have fewer effects on the motor systems because they block serotonin 5HT2A receptors along with D-2 receptors (Chapter 13).[38] D-1 and D-2 autoreceptors also regulate release of dopamine from presynaptic nerve terminals. Polymorphisms in D-4 and D-5 dopamine receptors have been associated with ADHD in children.[27,39]

Serotonin Synapses

Serotonin plays a major role in the treatment of headache and depression, and a schematic of the machinery for serotonin synapses is shown in Figure **1–7** (Chapters 4 and 13). Serotonin synapses operate much like synapses for dopamine and NE. One difference is that the availability of tryptophan, the amino acid precursor of serotonin, controls the level of serotonin synthesis. Dietary tryptophan supplementation may stimulate serotonin synthesis, and this is thought to be the mechanism by which it reduces sleep onset time in some patients with insomnia.[40] Increasing tryptophan increases sleep while increasing the levels of neutral amino acids, which compete with tryptophan for membrane transport across the BBB, has the opposite effect. Sleep latency has been reported to be shorter in infants given higher amounts of tryptophan in formula.[41] Vesicular monoamine transporters (VMAT) for serotonin and presynaptic serotonin transporters (SERT) for serotonin operate similarly to those in catecholamine synapses. SERT is a member of the monoamine transporter family and is a major target for selective serotonin re-uptake inhibitors (SSRIs) used commonly to treat depression.[42] Polymorphisms in SERT have been associated with familial psychiatric disorders and response to therapy in patients with major depression.[43] Postsynaptic receptors for serotonin are distributed in seven subtypes, most of which are metabotropic receptors that modify the second messengers cAMP or phosphoinositide turnover.[44] 5-HT-1 receptors are most important as targets for agonist therapy to treat migraine (Chapter 4), while multiple subtypes have been reported to mediate treatment for depression (Chapter 13).

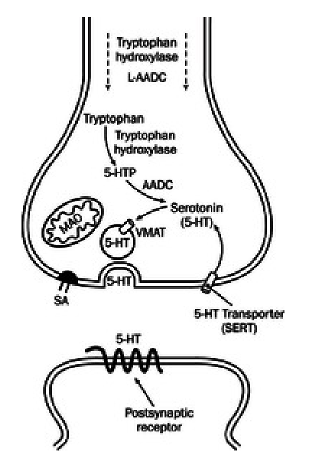




Figure 1–7.
Serotonergic synapse



Acetylcholine Synapses

Cholinergic neurons are involved in learning, memory, and cortical plasticity as well as in control of movement in the basal ganglia (Chapters 2 and 7), and the biochemical machinery involved in central cholinergic synapses is shown in Figure **1–8**. The cholinergic nucleus basalis is affected early in Alzheimer's disease and drugs that block acetylcholinesterase, the major enzyme that breaks down acetylcholine, are the primary therapy for cognitive and behavioral disorders in Alzheimer's disease.Acetylcholine is synthesized from choline and acetyl-coenzyme A derived from mitochondria, and these synapses are especially sensitive to oxidative stress and energy deficiency. Levels of acetylcholine can be influenced somewhat by levels of choline in the diet, and this nutrient is transported across the BBB by facilitated transport. Acetylcholine acts at both muscarinic and nicotinic receptors in the brain, and muscarinic receptors appear to be more important for normal cognitive function. Mutations in central nicotinic receptors are associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).[45]

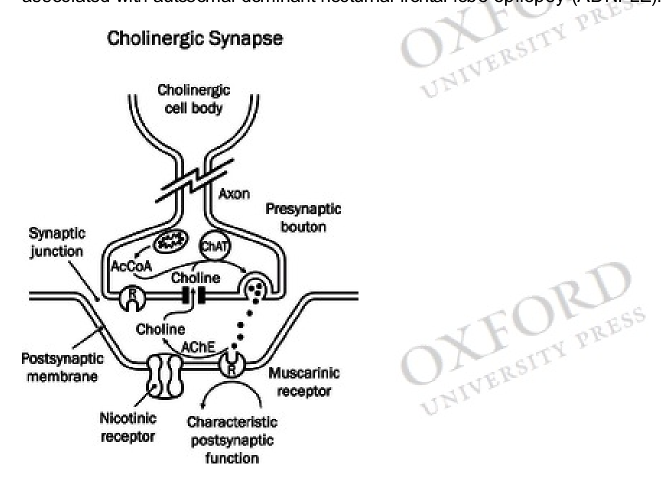




Figure 1–8.
Cholinergic synapse.

Blood Brain Barrier

The BBB is a target for pharmacotherapy because it impedes the exchange of molecules between the systemic circulation and the brain and it strongly influences or limits the effects of drugs in the central nervous system (CNS).[46] Abnormalities of the BBB are also involved in the pathogenesis of several disorders including vasogenic cerebral edema, multiple sclerosis (MS), HIV, and other infections (Chapters 6, 8, 16, and 17). The functional features of the BBB are attributable primarily to the tight junctions between brain endothelial cells that surround capillaries (Figure **1–9**).[47] Other functional components of the brain microvasculature include the basement membrane and foot processes of astrocytes, which are closely apposed to endothelial cells. However, the endothelial cells control the permeability of the barrier. Solutes are transported across the BBB either by diffusion through capillary endothelial cells or by facilitated transport. The rate of diffusion is determined primarily by blood concentration, protein binding, lipid solubility, and polarity (Table 1–2). More than 98% of large and small molecule drugs do not cross the BBB unless it is disrupted by tumors, infection, or inflammation. However, specific carrier-mediated and receptor-mediated transporters facilitate the entry of glucose, amino acids, and selected proteins such as insulin and transferrin (Table 1–3). One example of carrier-mediated transport is the large neutral amino acid transporter, which facilitates the entry of L-dopa into the nervous system. Neutral amino acids in the blood compete for this carrier as they do in the gastrointestinal tract, and the ingestion of dietary protein can reduce the effectiveness of L-dopa therapy for Parkinson's disease. Another example is the acetylcholine precursor choline, which is transported by an organic cation transporter. In animals it is possible to enhance the entry of large proteins or peptides such as growth factors by linking them to monoclonal antibodies directed against insulin or transferrin receptor mediated transporters.[46]

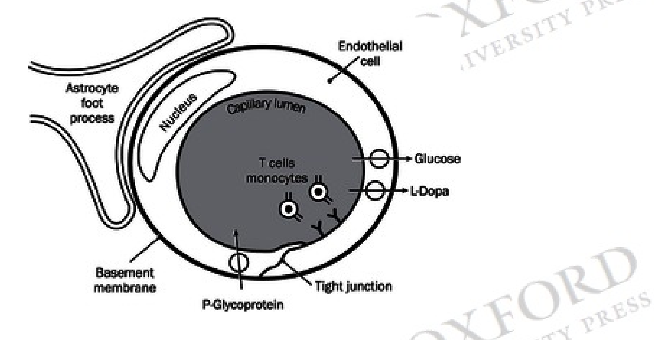




Figure 1–9.
Blood brain barrier formed by capillary endothelial cells.

Table 1–3 Transporters in the BBB		
Carrier mediated	**Receptor Mediated**	**Active Efflux**
Glucose (Glut1)	Insulin	P-glycoprotein (P-gp)
Large Neutral AA	Transferrin	ATP-binding Cassette B1
Cationic AA	Insulin-like Growth	ATP-binding Cassette C
Monocarboxylic AA	Factors 1, 2	ATP-binding Cassette G
Nucleosides	Leptin	Organic Anion
Organic Cation	Fc-IgG Fragment	Glutamic Acid SLC1
	Scavenger Receptor	Taurine

Abbreviations: AA = amino acid; SLC1 = solute carrier transporter 1.

Table 1–2 Factors Influencing the Rate of Drug Transport Through the BBB
Blood concentration
Protein binding of drug
Lipid solubility of drug
Polarity of drug
Size of capillary surface area
Affinity and density of transport carriers
Multi-drug transporters for drugs out of brain

Another set of transporters facilitates active efflux of drugs and toxins out of the nervous system.[48] These transporters are under active study as possible causes for reduced responsiveness to antiepileptic drugs in some patients. These transporters are products of genes such as the ATP-binding cassette 1 (ABC1) gene that code for a multidrug resistance (MDR) protein P-glycoprotein (P-gp) (Figure **1–9**). This protein was originally found to be responsible for decreased concentrations of drugs in cancer cells, and also facilitates the transport of antiepileptic drugs. P-gp as well as MDR genes have been reported to be overexpressed in the BBB of patients with refractory epilepsy.[49] Mice with knockout of the P-gp have higher brain concentrations of phenytoin than controls, and some data suggests that genetic variation in this protein may be associated with seizure intractability.[50,51]

Drug therapy that targets the function of the BBB is limited at this time. Corticosteroids improve BBB function in patients with vasogenic cerebral edema associated with brain tumors, but the mechanisms are unclear. Steroids have a similar effect on the BBB in patients with MS, but this therapy cannot be maintained for long periods. However, the monoclonal antibody containing the drug natalizumab can prevent inflammatory leukocytes from crossing the BBB.[52] Activated T cells and monocytes must cross the BBB from the systemic circulation to mediate pathogenic inflammation in cerebral white matter in MS. The interaction of integrin molecules on these inflammatory cells with integrin

receptors on the endothelium of the BBB is essential for entry into the brain. Natalizumab contains humanized monoclonal antibodies against these integrins and prevents their entry into the central nervous system. This ability to prevent the leukocytes from crossing the blood brain barrier is thought to be responsible for the drug's effectiveness as a disease-modifying therapy in MS (Chapter 8).

Neuromuscular Junction

The neuromuscular junction is a target for treatment of myasthenia gravis and other disorders of the neuromuscular junction as well as for therapy to relieve spasticity and movment disorders using injection botulinum toxin (Chapter 10).[53] Acetylcholine is synthesized as in central cholinergic neurons, but nicotinic receptors rather than muscarinic receptors activate muscle contraction at the neuromuscular junction (Figure **1–10**). Peripherally acting cholinesterase inhibitors such as pyridostigmine can increase levels of acethylcholine in patients with myasthenia gravis. Botulinum toxin is taken up into the presynaptic nerve terminal at specific receptors and is then internalized where it binds to the Snap 25 protein and cleaves it.[54] This prevents fusion of vesicles containing acetylcholine with the presynaptic membrane and the acetylcholine cannot be released to simulate muscle contraction.

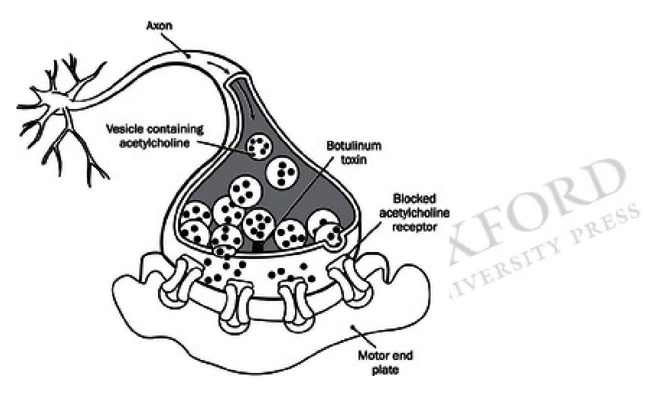




Figure 1–10.
Neuromuscular junction.

Absorption, distribution, metabolism, and elimination

Gastrointestinal Absorption

Most drugs used to treat neurologic disorder are administered orally, and factors that influence drug absorption by this route may have a major impact on the success of therapy. The amount of drug transferred from the gastrointestinal tract into plasma, or *bioavailability*, is determined by several biochemical factors (Table 1–4). Most drugs are relatively small molecules that are absorbed primarily by passive diffusion down a concentration gradient. The highest absorption rate occurs for small, highly fat-soluble, non-ionized drugs being exposed to a thin permeable, vascularized, membrane such as the small intestine. Drugs with larger molecular weights (> 900) are absorbed to a larger extent by vesicular pinocytosis. Absorption of water-soluble drugs is limited by the molecular size, whereas the absorption of most of the drugs used in neurology depends more heavily on the relative solubility of the compound in lipid membranes. By determining the ratio of the charged to uncharged form of the drug, pH influences lipid solubility (Figure **1–11**). In the stomach, the high concentration of hydrogen ions enhances the lipid solubility of weak acids by reducing the amount of ionized, water-soluble drug. On the other hand, basic drugs become ionized in the stomach making them polar and harder to absorb. They are thus better absorbed in the small intestine. This effect may be outweighed, however, by the effect of pH on drug solubility. For example, phenytoin, with a pK_a of approximately 8, is predominantly non-ionized in the stomach but is so insoluble in acid that very little absorption takes place. Although the pH of 7 in the duodenum causes more phenytoin to be ionized, the drug's greater water solubility at neutral pH allows more absorption.

Table 1–4 Factors Influencing Gastrointestinal Absorption of Drugs
Properties of drug
Solubility
Molecular size
Polarity
Bioavailability
Bioequivalency
Intersubject variability
Age
Diet
Ingestion of other drugs
Gut integrity, motility, blood flow



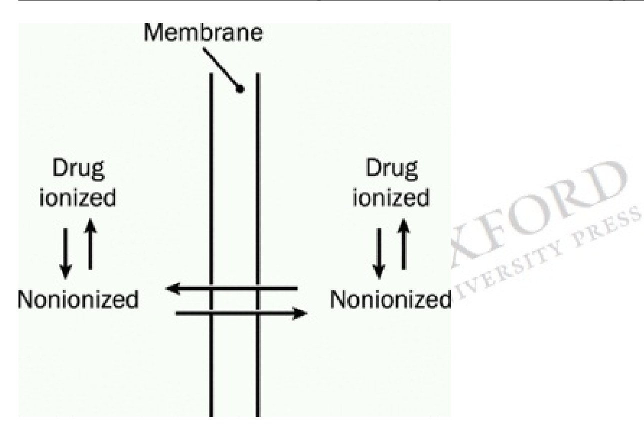




Figure 1–11.
Drug disposition across membranes.

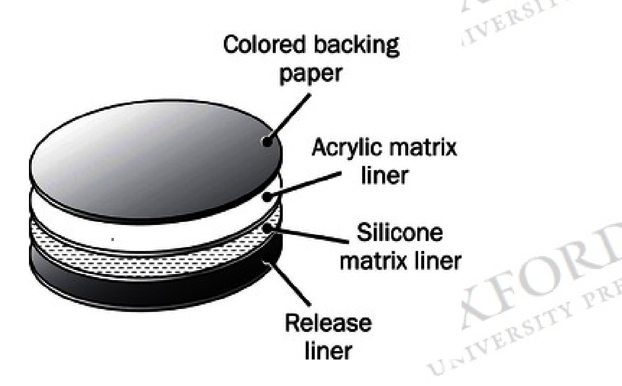
The *excipient*, or material with which the active drug is mixed, can influence intestinal absorption, and this may change the drug's relative ability to yield similar concentrations of drug in blood and tissues. The excipient can be used to create sustained or extended release formulations for certain drugs by combining them with insoluble matrices or gels using materials such as acrylics or chitins. For several anticonvulsants, including carbamazepine and phenytoin, clinically significant discrepancies in blood levels attained have been detected with administration of different formulations. These differences appear to be attributable to the effects of the drug excipient on absorption efficiency. Concurrent administration of food also unpredictably influences oral absorption of some drugs. Food tends to increase the absorption of water-insoluble drugs, and for certain drugs, gastric-emptying time (altered by the fat content of the meal or by disorders such as diabetes) may be important. Administration of drugs along with the tube feedings may sometimes result in reduced bioavailability. Food increases the systemic availability of drugs with a high hepatic extraction fraction, but the mechanism for this response is uncertain. An interesting, clinically important drug and food interaction has been recently delineated for absorption of L-dopa. L-dopa is absorbed from the gut primarily by a saturable carrier-mediated transport process. Neutral amino acids derived from ingested proteins compete with L-dopa for the carrier sites, and a high-protein diet reduces the bioavailability of L-dopa. A portion of the fluctuations observed in the efficacy of L-dopa resulting in the so-called on-off phenomenon is attributable to protein-induced variation in the amount of drug absorbed. However, some of the effect on performance may also be related to competition for transit across the BBB.[55] Development of effective sustained-release preparations has helped to overcome this problem.

Concurrent administration of multiple drugs, age, and specific systemic illness may also influence gastrointestinal absorption. Diseases associated with decreased cardiac output, malnutrition, and malabsorption may reduce the bioavailability of neurologic drugs. Age may also influence the efficiency of absorption. For example, it is difficult to use oral phenytoin in the first year of life because it is absorbed so poorly.

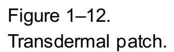
Other Drug Delivery Systems

Intravenous and intramuscular routes are often used in acute situations for loading with medication or when oral administration is impossible. The intravenous route is generally preferred because of pain and the potential unreliability of the intramuscular route. Refinements of intravenous drug delivery methods have been introduced for drugs that require stabilized blood levels for optimal therapeutic effect. Patient-controlled analgesia uses a programmed intravenous pump to allow patients to deliver a small fixed dose of opioid analgesics as needed to reduce pain.[56] The program prevents re-administration too frequently. This system produces less sedation and more consistent analgesia than conventional bolus injections. Prodrugs have also been developed to overcome problems with solubility of drugs for intravenous use. For example, fosphenytoin is a phosphate ester that is water soluble and is converted to phenytoin by blood and tissue phosphatases.[57] It can be administered intravenously or intramuscularly and lacks the burning and other side effects associated with the parent drug, which is poorly soluble and must be dissolved in a vehicle of propylene glycol and has a pH of 12. Intrathecal baclofen therapy delivered by programmable pumps has become a standard treatment for patients with severe spasticity and dystonia.[19]

Transdermal drug delivery systems make use of a drug-containing membrane held against the skin by an occlusive adhesive sheet (Figure **1–12**).[58] Drugs can be delivered by this route if they are potent, highly soluble in water and oil, and not irritating to the skin. When successful, this method delivers a steady amount of drugs into the blood with few peaks and valleys over prolonged periods. Transdermal patches for several medications, including scopolamine for motion sickness, clonidine, methylphenidate, fentanyl, the cholinesterase inhibitor rivastigmine, and the dopamine agonist rotigotine, are available.[59,60] The methylphenidate patch is recommended for a 9-hour period while the rivastigmine patch delivers the drug for approximately 24 hours. In addition to its convenience, which increases compliance and reduction in work for caregivers, the system may reduce variations in metabolism caused by the "first pass effect" seen when a large drug bolus is released into the bloodstream from parenteral delivery. A variation of the transdermal method uses iontophoresis to electrically charge drug molecules such as proteins that do not pass through the stratum corneum easily.[61]






Figure 1–12.
Transdermal patch.

Rectal administration can also be a convenient route for rapidly delivering certain drugs such as anticonvulsants for acute seizures. Rectal formulations of diazepam produce a rapid blood level of drug with few serious side effects, and anticonvulsants such as valproate and paraldehyde also can be administered through the rectal mucosa.[62,63] Several drugs can also be administered through oral and nasal mucous membranes, providing a rapid onset and a more stable blood level, but a relatively high lipid solubility is required for these routes to be effective. Lipid-soluble opioids such as fentanyl and methadone can be absorbed by the sublingual route, and morphine can be absorbed from buccal administration. A fentanyl lozenge is available for cancer pain. The opioid sufentanil has been administered to children in nasal drops[64] and butorphanol, a synthetic morphine analogue, is available as a nasal spray.[65] This method reportedly produces longer-lasting analgesia than the intravenous route. The migraine medication zolmitriptan is also available in this formulation.[66] Buccal administration of midazolam has been reported to be as effective as rectal diazepam for treatment of acute seizures, and this drug has also been administered by the nasal route.[67] A preparation of clonazepam in a wafer formulation that dissolves rapidly in the mouth is another alternative to intravenous or rectal administration of anticonvulsants for rapid control of seizures.

Drug Distribution

After absorption into the systemic circulation, distribution of a drug into tissue is an important determinant of the rapidity of onset and duration of its action (Figure **1–13**). The rate and differential distribution of a drug depends on its physicochemical properties (Table 1–5). The volume of distribution (Vd) is the theoretic volume of water into which a known dose of drug must be dissolved to achieve a certain concentration. The Vd can be calculated according to the formula:Vd = (D/C)W, where Vd = volume of distribution, D = loading dose, C = change in serum concentration, and W = weight. Comparing the Vd of a drug to the physiologic volumes of the various water compartments of the human body gives an indication of how extensively the drug is distributed throughout the body. The Vd determines the loading dose needed to attain therapeutic drug levels rapidly in situations such as status epilepticus. The apparent Vd, or the ratio of the amount of drug in the body to the serum concentration of the drug, is relatively large in highly tissue-bound drugs. Drugs with lower Vd will mainly be stored in blood (approx. 5 L in a 70 kg person). As the Vd increases, the drug gets stored in larger water compartments in the body, such as extracellular fluid (14 L), total body water (42 L) or tissues (> 200 L). Protein binding in plasma is a major factor influencing drug distribution throughout the body. Many drugs, as well as endogenous compounds, bind reversibly to albumin and to a lesser extent to other serum proteins such as α-1 acid glycoprotein. Competitive displacement of highly bound drugs (e.g., phenytoin) from protein-binding sites by other drugs or endogenous substances may cause rapid changes in free drug levels. The extent to which drugs compete for albumin sites is difficult to predict. For example, carbamazepine is predominantly protein bound, but it does not displace drugs such as phenytoin to a significant extent. The effect of disease or other drugs on therapeutic effect may also be unpredictable.

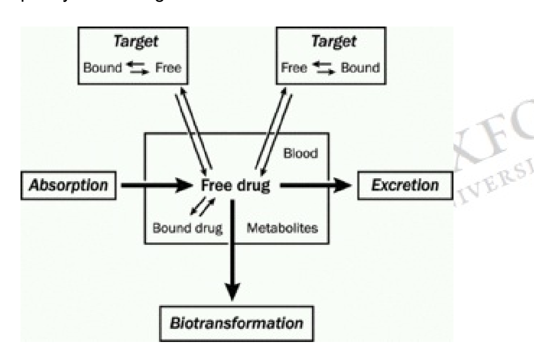




Figure 1–13.
Drug distribution.

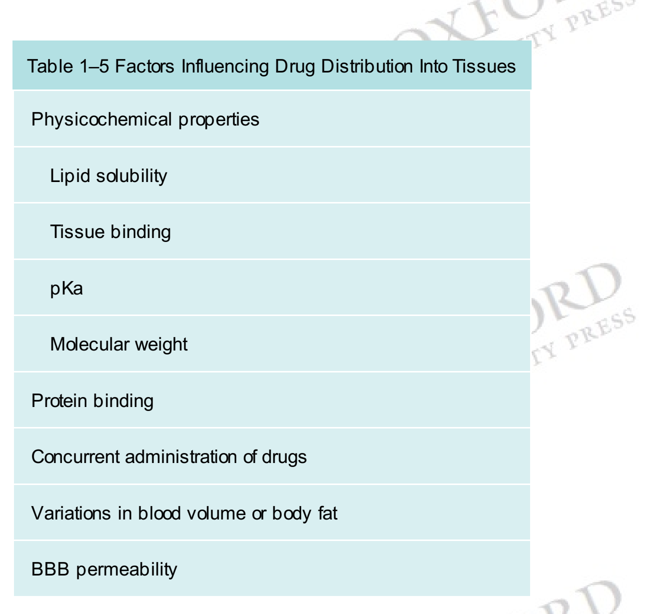




Table 1–5 Factors Influencing Drug Distribution Into Tissues
Physicochemical properties
Lipid solubility
Tissue binding
pKa
Molecular weight
Protein binding
Concurrent administration of drugs
Variations in blood volume or body fat
BBB permeability



Changes in the body composition may alter the distribution and therapeutic effects of neurologic drugs. One example of the impact of body composition changes in drug distribution is pregnancy. An expansion of the volume of distribution in pregnancy generally leads to lower serum levels of drugs such as anticonvulsants, and frequent monitoring is necessary to maintain a therapeutic level.[68] Drugs that are lipid soluble and poorly protein bound are most likely to cross the placenta and be distributed in the fetus. Postpartum drug distribution to breast milk is highest for lipid-soluble drugs that are alkaline and not protein bound. Fat may become a reservoir for lipid-soluble neuroactive drugs, and obesity may alter the clinical response. Redistribution of ultrashort-acting barbiturate anesthetics from fat may be prolonged lengthening recovery from anesthesia. The volume of distribution for drugs such as benzodiazepines and phenytoin increases markeedly in very obese subjects. The mechanism for this observed effect does not appear to be fully explained by the lipophilic properties of the drugs.

Drug-Receptor Interactions

The effect of a drug is strongly determined by its interaction with specific target molecules such as receptors or enzymes, and these interactions are typically modeled using the *law of mass action* involving a drug ligand (Drug) and a receptor (R) (Figure **1–14**). This interaction can be described as an equilibrium between the bound drug ligand-receptor and the dissociated drug ligand and receptor:

$$\mathrm{Drug} + \mathrm{R} \leftrightarrow \mathrm{Drug} \cdot \mathrm{R},$$

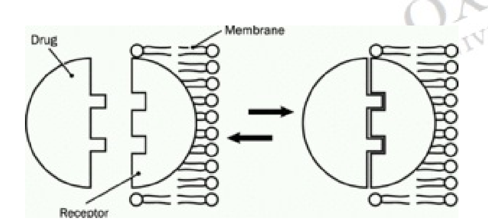


Figure 1–14.
Drug-receptor binding.



An equilibrium dissociation constant. (Kd) is defined as K_D = [Drug][R]/[Drug · R].

The fraction of drug bound to the receptor is related to this dissociation constant so that:

$$\%\mathrm{Bound} = 1/1 + \mathrm{K_D}/[\mathrm{Drug}].$$

The K_D generally equals the drug concentration at which 50% of the receptors are occupied. A lower dissociation constant (K_D) implies that the drug binds to the receptor with greater affinity and will have a stronger physiological effect at the same dose than drugs with higher K_Ds. When plotted as a curve relating fraction bound versus log concentration of drug, the data for drug-receptor interactions usually resembles the traditional log dose response curve shown in Figure **1–15**. In the dose response curve, the maximal effect of the drug is referred to as its *efficacy*. If the efficacy of two drugs are similar as shown in the figure, then their *potencies*, or drug concentrations needed to produce a half maximal effect, can be compared and occur when 50% of receptors are occupied and [Drug] = Kd. Potency is the more useful measure of the effect of drugs because it applies to submaximal doses more likely to be within the *therapeutic window* of concentrations in which it is effective but does not produce toxicity.

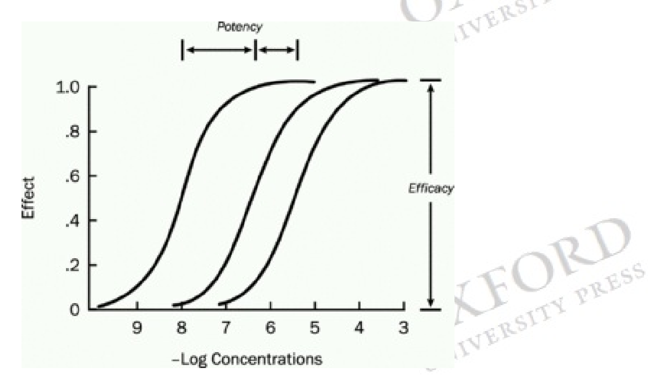


Figure 1–15.
Drug-dose response curves.

Drug Metabolism

The lipid-soluble drugs most commonly used for neurologic disorders are generally metabolized to create more polar, less active compounds, which can be eliminated more efficiently by the kidney.[69] Hydroxylation, oxidation, dealkylation, and deamination reactions are the most common metabolic transformations. These so-called phase I reactions are sometimes followed up by conjugation to compounds, such as glucuronic acid or an amino acid, that enhance water solubility (phase II reactions). The liver is the major site of metabolic transformations, but the lung, gut, and kidney may also contribute. The majority of drugs are metabolized in the liver by the mixed-function hepatic cytochrome P-450 (CYP) oxygenases, but other mixed-function oxidases also participate.[69] Similar enzymes have been identified in the brain, although their contribution to metabolism is not clear.[70] The CYP enzymes are a super-family of mixed function, iron-containing, enzymes that generally add a functional group (i.e., hydroxyl) to the structure of lipophilic endogenous molecules, drugs, and other environmental chemicals, rendering them more polar, less lipophilic, and hence easier to excrete.[71] Multiple enzymes may contribute to metabolism of a single drug. The genetic control of activity of these enzymes is complex and may account for clinically important variability in these reactions.[72] More than 18 families and 57 genes for CYP enzymes have been identified in humans but most clinically relevant drugs are metabolized by members of the CYP1, CYP2, and CYP3 families. For example, 90% of the metabolism of phenytoin is performed by the CYP2C9 enzyme and carbamazepine is metabolized mostly by CYP3A4. Concomitant administration of drugs that are preferred substrates for the same iso-enzyme alters the metabolism rate of each individual drug (i.e., drug interactions). One example encountered in patients with spinal cord injury is inhibition of tizanidine metabolism by ciprofloxacin via CYP450 1A2, which may significantly increase the plasma concentrations and pharmacologic effects of tizanidine.[73]

Age, systemic illness, and concurrent use of other drugs that induce biotransforming enzymes may alter drug metabolism. For example, phenobarbital is metabolized more rapidly in infants than in adults so the dose per kilogram needed in infants is more than twice as high. Powerful enzyme inducers such as phenobarbital and other drugs with aromatic structures increase the activity of P-450 oxidases in liver, which in turn stimulates the metabolism of many other drugs. For example phenobarbital dramatically enhances the metabolism of cyclosporine required to attain therapeutic levels for immunosuppression. Another example is the ability of valproate to increase serum phenobarbital levels by an average of 50% when the two drugs are given concurrently.[74] Biotransformation reactions can also enhance the therapeutic efficacy of a drug. For example, the major pathway for metabolism of the anticonvulsant carbamazepine is formation of a 10,11 epoxide by P-450 mixed-function oxidase, and this epoxide metabolic also has anticonvulsant properties. Carbamazepine generally induces its own metabolism, and after several weeks of treatment the dose may need to be increased to maintain a therapeutic level.[75]

Drug Elimination

The kidney is the major organ responsible for elimination of unchanged polar drugs or lipophilic drugs that have been metabolized to make them less hydrophobic (Table 1–6). The concept of *clearance* of a specific compound is used to describe the efficiency of drug elimination and is expressed as the volume of blood cleared of drug per unit time (ml/min). Typically a constant fraction of the drug is removed from the plasma by the kidney. Excretion is primarily done by the kidneys, either by filtration and/or secretion into the urine (e.g., Baclofen, dantrolene, gabapentin). For drugs eliminated mainly by filtration, renal blood flow and the glomerular filtration rate are the major determinants of clearance rates. Some drugs are secreted into the bile and are excreted through feces (e.g., benzodiazepines, cannabinoids). In the case of biliary excretion, enzymes in the gut can convert the metabolically inactive drug into the original lipophilic active drug, which is then reabsorbed, a process called eneterohepatic recirculation, which

dramatically prolongs the drug action and excretion time.

Table 1–6 Factors Influencing Drug Elimination
Renal blood flow and glomerular filtration rate
Protein intake
Renal tubular secretion efficiency
Multiple drugs administered concurrently
Kidney or liver disease
Presence of enterohepatic circulation



In patients with renal failure, multiple pathophysiologic mechanisms including reductions in glomerular filtration rates, low plasma albumin levels, concurrent administration of a large number of medications, and treatment with dialysis all influence drug clearance rates.[76] Experience with phenytoin metabolism in uremic patients demonstrates the issues that must be considered in analyzing the effects of renal failure on drug clearance. For a given dosage, total serum phenytoin levels are generally lower in uremic patients, but free serum phenytoin levels rise because of decreased protein binding.[77] There is no change in the clearance of the unbound fraction, and free levels remain relatively stable. Reduced clearance of hydrox-ylated phenytoin may contribute a modest anticonvulsant effect.[78]

Pharmacokinetics

Absorption, distribution, metabolism, and elimination together determine each drug's pharmacokinetic (PK) profile. Both drug and host factors determine the plasma level of drug attained, the duration of sustained peak drug levels, and the magnitude of fluctuations in drug levels over time. An appropriate dosage range for administration of each drug is typically derived from population studies. The *half-life* of a drug is the time period during which its plasma concentration falls to 50% of the peak level after a single dose (Figure **1–16**). The ty_2 can be measured experimentally with repeated sampling in individual patients, or alternatively it can be estimated from fewer repeated measurements in a large group of patients. Computer programs have been developed to calculate ty_2; sophisticated PK models may take into account a variety of factors that determine plasma levels, including volume of distribution, tissue binding, and clearance. The Food and Drug Administration has recommended the application of model-based drug development (MBDD) to better predict the behavior of drugs early in development because less than 10% of new compounds that enter clinical trials ultimately make it to market.[79]

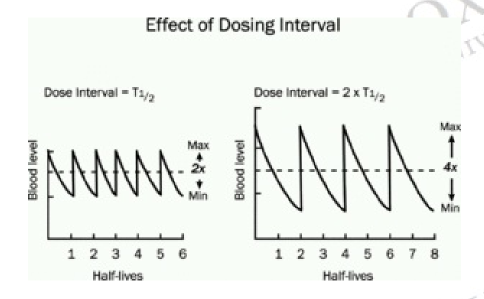


Figure 1–16.
Effect of dosing interval.

The $t_{1/2}$ indicates how frequently doses must be given to minimize fluctuations in blood levels (Figure **1–16**). Several drugs with relatively short $t_{1/2}$s, including sodium valproate, carbam-azepine and L-dopa, are available in extended release formulations that minimize fluctuations in blood level. The $t_{1/2}$ is a good indicator of the amount of time required to reach steady-state drug levels with maintenance drug dosages; after initiation of therapy, steady-state levels are attained after four to five half-lives. Biologic $t_{1/2}$ is the length of time required to half the initial drug effect. For drugs with low volumes of distribution, the plasma tyg and biologic $t_{1/2}$ are close, but in the case of drugs with large volumes of distribution that get deposited in the tissues and continue to exert their action, or for drugs that have metabolites with similar pharmacologic activity, the biologic $t_{1/2}$ (important for true drug activity) is much larger than the plasma $t_{1/2}$.

Most drugs used in neurology follow so-called *first order kinetics* of disposition of drug from the bloodstream in the therapeutic range, meaning that a constant *percentage* of drug is metabolized per unit time over the range of plasma concentrations (Table 1–7). Another way of describing first-order kinetics is that the rate of metabolism increases in direct proportion to the amount of drug available. This situation generally arises from an interaction between a drug and an enzyme when binding sites for the drug are well below saturation. In contrast, for drugs with *zero order kinetics*, a constant *amount* rather than a constant percentage of drug per unit time is metabolized. For drugs with zero-order kinetics, the rate of metabolism is fixed and independent of the amount of drug, and the enzyme responsible for metabolism is usually near saturation. Ethanol is a compound with zero-order kinetics at blood levels commonly reached by social drinkers (Figure **1–17**). Phenytoin is metabolized by first-order kinetics at low to moderate therapeutic blood levels, but demonstrates zero-order kinetics at higher to toxic blood levels (Figure **1–18**).80 The enzyme for hydroxylation of phenytoin is only partially saturated at low to moderate levels (<15 μg/mL) but becomes saturated at higher levels. As the dose is increased, plasma concentrations rise, and the apparent ty2 increases because of a shift from first-order to zero-order kinetics. This pattern is described as Michaelis-Menton kinetics. This shift in kinetics in the middle of the therapeutic range of blood levels can at times make phenytoin blood levels hard to regulate. As enzyme saturation is approached, small increments in dosage can lead to abrupt rises in serum levels into the toxic range. Also, when blood levels reach the toxic range, the rate of decline of levels back into the therapeutic range is correspondingly prolonged.

Table 1–7 Drug Kinetics Terminology

Term	Definition
Pharmacokinetics (PK)	Relationship between drug dosage and plasma concentration of drug over time
Pharmacodynamics (PD)	Relationship between plasma concentration and drug effects
First-order kinetics	The rate of drug metabolism is proportional to the amount of drug; a fixed *percentage* of drug is metabolized per unit time
Zero-order kinetics	The rate of drug metabolism is fixed and independent of drug concentration; a fixed *amount* of drug is metabolized per unit time
Half-life ($t_{1/2}$)	The time period over which a drug's plasma concentration falls to 50% of peak level after a single dose

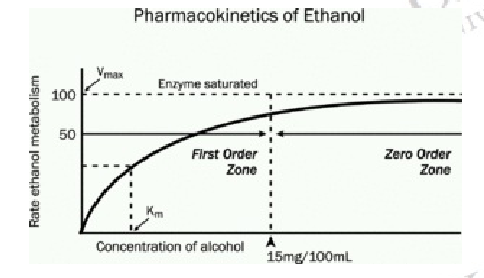


Figure 1–17.
Pharmacokinetics of ethanol.

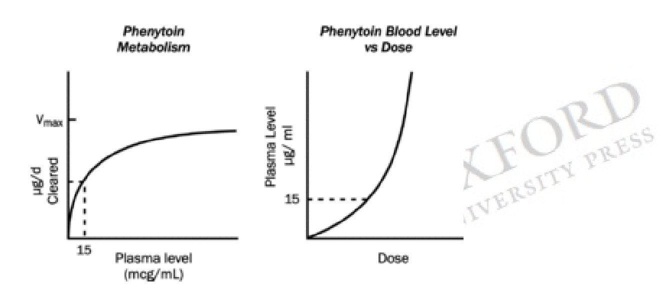


Figure 1–18.
Dose-related kinetics of phenytoin.

Therapeutic Drug Monitoring

Most drugs are useful within a therapeutic window of blood concentrations that are high enough to be active but low enough to avoid toxicity. However, even small amounts of some drugs can produce toxicity and the useful upper range may vary based on genetic polymorphisms in molecular targets.[69,81] Therapeutic monitoring of levels of drugs in blood is routinely used in the care of patients with epilepsy but not in most other patients with neurologic disorders. There is significant intersubject variability in drug concentrations attained after administration of routine drug dosages. Although some studies suggest that this practice does not improve compliance, seizure control, or avoid side effects, it is useful in many patients.[82,83] Indications for measuring drug levels include establishing steady-state concentrations and determining the impact of a new drug formulation, dosage changes, and addition or elimination of other drugs. Measurement of drug levels may be especially valuable for drugs with a narrow therapeutic range, or in patients who are pregnant or very young or very old and cannot adequately report side effects.[84] Other indications include reemergence of symptoms, kidney or liver disease, pregnancy, and evaluation of possible toxicity. Timing of sampling will influence results obtained; peak levels may be most helpful for assessment of toxicity while trough levels may provide more predictable information about steady-state levels. When drug levels are measured, values usually reflect the total serum concentration, which includes both protein-bound and free drugs. In most cases, these measures accurately reflect free-drug levels. However, free-drug levels of highly bound drugs such as phenytoin may be useful in critically ill patients who may have changes in protein binding or if there is unexpected drug toxicity or lack of efficacy.[85] New assays of anticonvulsant drugs in saliva are being developed that may replace some blood monitoring methods, which are associated with pain and difficulty obtaining a sample especially in small children.[86]

Pharmacogenetics

Multiple steps that control the absorption and metabolism of drugs, their entry into the nervous system, and their activity at specific targets are under genetic control. The area of pharmacogenetics examines how genetic differences influence the outcome of therapy for specific disorders and virtually every area of neurology and psychiatry can be evaluated from this perspective (Table 1–8).[87–89] Multiple polymorphisms in CYP genotypes have been implicated in changes in drug PK, especially in the metabolism of anticonvulsants. As described previously, polymorphisms in genes for multidrug efflux transporters have been proposed to increase susceptibility to drug resistant epilepsy. Genetic polymorphisms in major targets for anticonvulsants such as the voltage dependent sodium channels have been linked to the need for higher than average doses of phenytoin and carbamazepine.[72] Mutations in the α-1 subunit of the SCN1A gene also cause the syndrome of SMEI (Dravet syndrome), which is poorly responsive to sodium channel blocking anticonvulsants such as carbamazepine.[90] Recent evidence suggests that these patients respond better to levetiracetam, which acts by an independent mechanism of action on synaptic vessel protein 2A (SV2A).[91] Similar genetic changes in calcium and chloride channels, as well as glutamate and GABA receptors, may determine the spectrum of anticonvulsant activity in other patients with epilepsy.[1] Adverse reactions to drugs may also be partially under genetic control, and serious skin hypersensitivity to carbamazepine has been associated with a polymorphism in the tumor necrosis factor alpha (TNFa) gene.[92] This information indicates that genetic factors influence both the metabolism and mechanism of action of drugs, and suggests that therapy can be made more specific for individual patients in the future using a genetic

approach.

Table 1–8 Candidate Genes Affecting Drug Action or Metabolism

Gene/Protein	Function	Drugs
CYP2C19	Hydroxylation	Phenytoin, Valproate
CYP3A4	Hydroxylation	Carbamazepine
UGT1A4	Glucuronidation	Lamotrigine, Valproate
p-Glycoprotein	Multi-drug transporter	Multiple drugs
SCN1A	Sodium channel	Phenytoin, Carbamazepine
GABRA1	GABA-A receptor	Benzodiazepines, Phenobarbital
CLCN2	Voltage-gated Cl channel	Benzodiazepines



Toxicity of neuroactive drugs

Adverse effects are an important determinant of the usefulness of drugs and compliance in individual patients. One study showed that one quarter of patients with new onset epilepsy discontinued the first drug prescribed for them because of adverse side effects such as skin rashes.[93] The *therapeutic index* is the relationship between the average therapeutic dose and the toxic dose, but within a group of patients receiving the same drug at the same dose, there can be significant variation in the frequency and severity of adverse reactions. Adverse reactions can be divided into dose-dependent effects, explained by the drug's mechanism of action, and idiosyncratic events, which are unrelated. Idiosyncratic responses occur unpredictably in a small minority of patients, but they account for most of the very serious or fatal events.[94] Genetic factors may account for enhanced susceptibility to both types of side effects. This section examines some important clinical syndromes of neurologic dysfunction and systemic toxicity.

Cognitive and Behavioral Changes

Hypnotics, anticonvulsants, neuroleptics, and antidepressants can all impair attention, memory, mood, and overall cognitive performance.[95] Barbiturate anticonvulsants have been shown to impair mood and cognition in both children and adults, which is probably related to their ability to enhance GABA-mediated neuronal inhibition.[96] A family history of depression may predispose to depression associated with phenobarbital in children.[97] Nonbarbiturate anticonvulsants can also produce impairment in some patients. Topiramate has been reported to impair verbal cognitive function in patients at high doses, possibly related its inhibition of the AMPA-type glutamate receptor that is involved in learning and memory. Carbamazepine does not appear to affect intelligence in children but may have a modest effect on memory. Valproate appears to have less effect on cognitive performance than phenytoin or carbamazepine, but in a few susceptible patients may cause an encephalopathy. In children, it is sometimes difficult to distinguish the adverse effects of drugs from the learning disabilities attributable to poorly controlled seizures or underlying neurologic disorder. Potential cognitive side effects of anticonvulsants need to be weighed against the effects of poor seizure control on cognition. Other noteworthy effects of medications include amnesia associated with the muscarinic antagonist scopolamine used for motion sickness and benzodiazepine agonists such as zolpidem for sleep or midazolam for sedation.[98] Central cholinesterase inhibitors such as donepezil used for Alzheimer's disease can cause hallucinations and delirium in some patients, and the dopamine agonists ropinirole and pramipexole have been associated with excessive gambling and sexual behavior in patients with Parkinson's disease.[99]

Appearance, Body Weight, and Metabolism

Drugs that induce changes in weight or appearance can strongly reduce compliance with a chronic drug regimen. Phenytoin is well known for causing gum hypertrophy, excessive body hair, and facial coarsening, while valproate can produce reversible hair loss as well as substantial weight gain.[100,101] Weight gain can also follow therapy with neuroleptic drugs, including the second generation atypical neuroleptics, antidepressants, and the antimigraine drug cyproheptadine. Second generation antipsychotic drugs may have a greater propensity to cause severe weight gain with hyperlilpidemia and type II diabetes mellitus, and careful monitoring is important.[102] On the other hand, topiramate often causes decreased appetite and weight loss and is being prescribed for that purpose in some cases, such as patients with binge-eating disorders.[103] This effect of topiramate may relate to blockade of glutamate receptors in the hypothalamus where glutamate normally stimulates appetite. Anticonvulsants and other drugs that activate oxidative systems also promote the catabolism of vitamin D metabolites causing a relative vitamin D deficiency. Patients on these drugs for a long period need to be monitored for bone density to detect osteomalacia and osteoporosis, especially if they are also inactive.[104] Another side effect caused by SSRI and tricyclic antidepressants as well as carbamazepine, oxcarbazepine, and levetiracetam is the syndrome of inappropriate antidiuretic hormone (SIADH).[105] Syndrome of inappropriate antidiuretic hormone-induced hyponatremia is associated with headache and mental status changes and cerebral edema.

Skin Disorders

Drug-induced skin reactions are relatively common for some groups of drugs such as anticonvulsants, but vary widely in their manifestations and severity from self-limited rashes to life threatening disorders such as DRESS (drug rash, eosinophilia and systemic symptoms), Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).[106] Anticonvulsants can also rarely induce or activate systemic lupus erythematosis.[107] Benign maculopapular rashes occur in approximately 6%–15% of patients started on phenobarbital, phenytoin, carbamazepine, oxcarbazepine, or lamotrigine, and switching to another member of this group carries an increased risk of another rash.[108] These rashes appear to be immune mediated, and the incidence is higher in other family members, suggesting a genetic susceptibility.[109,92] The incidence of rashes and other idiosyncratic reactions is higher in children than adults because of faster rates of CYP metabolism and higher doses per body weight. Production of large amounts of reactive arene oxide and other metabolites from anticonvulsants with aromatic ring structures may present a greater stimulus to the immune system, and low starting doses and slow escalation of the dose may reduce the incidence of rashes.[108,110] The incidence of rashes may be lower for levetiracetam, gabapentin, valproate, topiramate, and vigabatrin, which have different chemical structures.[108] However, concurrent administration of valproate and lamotrigine markedly increases the risk of allergic rashes from 8% with lamotrigine alone to 30% with both drugs.[111] This may relate in part to the fact that administration of valproate causes a 50% reduction in metabolism of lamotrigine.[112]

Drug rash, eosinophilia and systemic symptoms, which is also known as anticonvulsant hypersensitivity syndrome because it was first described for these drugs, includes a diffuse maculopapular rash and erythroderma, fever, atypical lymphocytosis, arthralgia, lymphade-nopathy, and involvement of other organs including the liver, kidneys, heart, and lungs.[113,114] Several hypotheses have been advanced to explain DRESS, including accumulation of toxic drug metabolites, graft versus host disease, antibody production, and viral infections. Stevens Johnson Syndrome and TEN are distinguished from DRESS by the appearance of blistering of the skin with purpuric macules and mucosal involvement.[115] Stevens Johnson Syndrome and TEN are distinguished from each other by the degree of skin detachment, which is more than 30% in TEN. Mortality is higher in older individuals than children and is related to the degree of skin involvement. The overall incidence of SJS and TEN is approximately one case per million and approximately half are caused by more than 100 drugs. Concurrent viral illness, collagen vascular disease, and genetic factors may also contribute, and one study reported a

high incidence of SJS in patients on phenytoin being treated with cranial radiation for brain tumors.[116] Recent data suggest that the incidence of SJS and TEN during the first two months of therapy is between 1–10 per 10,000 new users for carbamazepine, lamotrigine, phenyotoin, and phenobarbital and lower for valproate.[117,118] The incidence of SJS is higher in children than adults. In addition to medical and surgical treatment for complications of loss of skin coverage and involvement of the eyes and mucous membranes, intravenous immunoglobulin is often given to these patients. Preliminary reports also suggest that the antitumor necrosis factor antibody infliximab may also be helpful.[119]

Hematologic Disorders

Many drugs occasionally produce bone marrow suppression involving one or multiple cell lines and, rarely, aplastic anemia, and the mechanism has been attributed to toxic metabolites of drugs an immune response or a combination of these two mechanisms.[106,120] The incidence of aplastic anemia in patients taking carbamazepine is estimated at 1/50,000 to 1/200,000 while the incidence for the anticonvulsant felbamate is 10 times higher. There is no evidence that routine monitoring of blood counts is effective in decreasing the incidence of drug-induced aplastic anemia. Hemolysis or thrombocytopenia may result from drug-induced autoimmune responses, and eosinophilia and lymphade-nopathy may reflect hypersensitivity reactions to drugs such as phenytoin. Macrocytic anemia may rarely result from anticonvulsant-induced folate deficiency and platelet dysfunction may result from valproate therapy.[121]

Liver Disease and Pancreatitis

Many drugs cause hepatic necrosis or milder immune-mediated liver toxicity.[122] The older anticonvulsants and lamotrigine have been associated with low rates of reversible liver dysfunction, including cholestatic jaundice, but valproate and felmbamate can cause fatal hepatic failure with an incidence of about 1/30,000 in the general population.[123] For children less than two years of age on polytherapy with some evidence of a metabolic disorder the incidence is much higher at about 1:500.[124,125] Some evidence suggests that two specific oxidation metabolites of valproate catalyzed by CYP2C9 play a role in hepatic necrosis, and this enzyme can be induced by administration of other anticonvulsants.[126,127] Higher rates of metabolism by CYP enzymes in young children as well as relatively higher doses of drug per unit weight are thought to contribute to enhanced risk below the age of two years. Metabolic disorders involving mitochondrial oxidation and antioxidant pathways are prevalent in children with serious hepatic reactions to valproate and may predispose to toxicity from metabolites of this drug.[125] Similar mechanisms may be involved in the pathogenesis of pancreatitis associated with valporate, which occurs with an incidence of 1:40,000.[128] The mechanism for felbamate induced hepatic necrosis is not understood but may involve production of toxic aldehyde metabolites of the drug.[129]

Visual Reactions

Two important ocular reactions to neurological drugs are acute secondary angle-closure glaucoma from topiramate[130,131] and visual field constriction secondary to prolonged vigabatrin administration.[132,133] Visual field loss attributable to vigabatrin (VAVFL) occurs in about 20% of patients on the drug with males more affected than females, and visual acuity and color vision is not affected. There does not seem to be a relationship between the length of therapy or total dose and the incidence or severity of VAVFL, suggesting that specific predisposing factors may exist.

Decreased Seizure Threshold

A few drugs are associated with a reduction in the seizure threshold in some patients, especially those with certain epilepsy syndromes. Although comparative data are limited, chlorpromazine appears to be associated with a small increased risk for increasing seizures while the risk for second-generation neuroleptics such as haloperidol, pimozide, and risperidone is lower.[134] Stimulant medications such as methylphenidate may lower the seizure threshold in patients with abnormal electroencephalograms, but have little effect in otherwise normal patients.[135] The newer stimulant atomoxetine seems to have little risk of provoking seizures.[136] Baclofen, which is used widely to control spasticity may precipitate seizures in some young children with cerebral palsy who are predisposed to seizures.[137] Anticonvulsants can also paradoxically provoke seizures in patients with epilepsy. For example, concurrent treatment with valproate and clonazepam can precipitate absence status epilepticus in susceptible children. Carbamazepine is well known to precipitate absence status in some patients with spike-wave activity on their electroencephalogram and also worsen seizures in patients with juvenile myoclonic epilepsy (JME).[138–140] Very high levels of anticonvulsants such as phenytoin are also reported to cause seizures, as are toxic levels of tricyclic antidepressants.[141,142] Even more commonly, seizures are precipitated by rapid withdrawal of anticonvulsants in patients with underlying seizure disorders. Antibiotics such as high doses of penicillin and related drugs such as imipenem, a betalactamase, can also cause seizures by specific effects on GABAergic inhibitory neurotransmitter systems.[143] The immunosuppressive drugs cyclosporine and tacrolimus (FK-506) are also associated with seizures and encephalopathy including posterior leukoencephalopathy in patients undergoing organ transplantation.[144,145]

Movement Disorders

Drugs that modify the dopamine system are most likely to cause movement disorders as side effects. Dyskinesias associated with treatment of Parkinson's disease are an important clinical problem (Chapter 2).[146] Drug-induced Parkinsonism, dystonia, and akasthisia (motor restlessness) are also common in patients treated with neuroleptic medications such as phenothiazines and butyrphenones, but movement disorders are less of a problem with second-generation atypical antipsychotic agents (Chapter 13).[147] These side effects of dopamine receptor blockade generally respond to anticholinergic drugs. Acute dystonic reactions can also occur in children or older individuals treated for medical conditions with antiemetic drugs such as prochlorperazine or metaclopromide, which are milder dopamine blockers, and they usually respond to acute treatment with antihistamines or anticholinergics.[148] The calcium antagonists flunarizine and cinnarizine can also produce dyskinesias, probably also by acting on the dopamine system. Dystonia, choreiform movements, and orofacial dyskinesias have been observed in patients given high doses of phenytoin and other anticonvulsants. Patients who already have injuries or disorders of the basal ganglia are predisposed to these reactions.[149] Treatment with stimulants such as methylphenidate for ADHD has been associated with motor tics, but double-blind evaluation indicates that they are probably not initiated by the drug.[150] They appear to be safe if needed to treat patients who have both Tourette syndrome and ADHD, and do not produce long term worsening of the disorder.

Tardive Dyskinesia

Tardive dyskinesia (TD), is a serious movement disorder that develops in patients treated with dopamine antagonist drugs, especially antipsychotics, for more than one year and is irreversible in some cases.[151] Typical manifestations include rapid facial and lingual tics or dystonic facial movements, akathisia, and choreoathetoid limb movement. The incidence has fallen to about 1% in younger patiens and around 5% in elderly patients with the wider use of second-generation atypical neuroleptic drugs. The underlying neurochemical abnormalities are uncertain; both D-2 dopamine-receptor supersensitivity and secondary degeneration of GABAergic synapses have been implicated. In addition, emerging evidence from pharmacogenetic studies suggests that allelic variants of genes associated with dopaminergic neurotransmission and hepatic metabolism of antipsychotics may affect vulnerability. Important unresolved issues include the effects of dosage, drug holidays, and the nature of the underlying disease on the development of tardive dyskinesia. When phenothiazines are discontinued, transient withdrawal dyskinesia may occur. The involuntary movements are the same as in tardive dyskinesia but, by definition, the symptoms resolve spontaneously within three months.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is another serious acute life complication of drugs that block dopamine receptors.[152] Clinical features include abrupt onset of muscular rigidity, fever, depressed consciousness, and autonomic dysfunction, typically occurring soon after initiation of treatment with neuroleptics. Patients with NMS may also have an elevation in serum creatine kinase with rhabomyolysis with myoglobinuria, as well as elevated transaminases and white blood cell count. The differential diagnosis includes infectious, psychiatric, metabolic, and toxic disorders including serotonin syndrome associated with administration of serotonin drugs and malignant hyperthermia. Serotonin

syndrome is also a serious disorder that includes tremor, myoclonus, brisk reflexes, confusion, tachycardia, and diaphoresis and fever with less rigidity and muscle involvement.[153] The serotonin syndrome can result from the use of serotonin re-uptake inhibiting antidepressants in combination with monoamine oxidase inhibitors or atypical antipsychotic agents such as resperidone or olanzapine.[154] The incidence of NMS has fallen to about .02% of patients treated with neuroleptics because it is generally recognized and treated earlier than in the past. High potency conventional antipsychotic drugs appear to carry greater risk than newer atypical neuroleptics, and certain alleles of the CYP2D6 metabolic enzyme have been reported to be associated with enhanced vulnerability.[152,155] Virtually all cases occur within 30 days of starting therapy or a major dose adjustment. Treatment includes immediate withdrawal of the drug and intensive medical support with intravenous fluids as well as administration of benzodiazepines, dopamine agonists such as bromocriptine or amantadine, and possibly dantrolene.[156] For mild cases, supportive care may be sufficient as the disorder is generally self-limited.

Cardiac Arrhythmias

Several medications used in psychiatry and neurology can cause life threatening arrhythmias in susceptible individuals.[157] In overdoses, cardiac arrhythmias are a major mechanism for the toxicity of phenytoin and tricyclic antidepressants.[158] Significant arrhythmias may occur with rapid intravenous administration of phenytoin, and loading doses should be administered cautiously with continuous electrocardiogram (ECG) monitoring. Rapid administration of large doses of barbiturates also may lead to depression of cardiac function and hypotension. Tricyclic antidepressants and antipsychotic drugs, which can prolong the corrected QT interval (QTc), increase the risk of polymorphic ventricular tachycardia (torsade de pointes).[159,160] This effect is enhanced in females and individuals with underlying heart disease. Newer serotonin reuptake inhibiting antidepressants and serotonin antimigraine drugs as well as the atypical neuroleptics also carry significant risks, especially in patients with genetic conduction abnormalities.[157] Mitoxantrone, an immunosuppressant used to treat MS can also cause heart failure probably related to its ability to form complexes with iron and increase oxygen free radical production.[161]

Influence of age on drug action

The Fetus and Anticonvulsant Teratogenesis

Anticonvulsants are given chronically to women in their childbearing years and are associated with birth defects. The incidence of congenital malformations in children born to epileptic mothers is about three times that in nonepileptic women (6% of drug-treated epileptics versus 4% of untreated epileptics and 2% of nonepileptics).[162] The fetal hydantoin syndrome, including intrauterine growth deficiency, mild mental retardation, a broad nasal bridge, coarse hair, hypoplastic nails, and occasional major anomalies of the heart and palate was the first to be described.[163] Some signs of the syndrome may occur in 5% to 10% of exposed infants. The risk is up to eight times higher if a combination of phenobarbital and phenytoin or another aromatic, enzyme-inducing anticonvulsant is used, and there appears to be overlap between the hydantoin syndrome and other anticonvulsant-induced disorders.[68,164] One mechanism thought to mediate anticonvulsant teratogenesis is excessive production and/or inadequate disposal of arene oxides and other of oxidative byproducts of anticonvulsant metabolism (Figure **1–19**).[165] This is similar to the mechanisms proposed for other side effects of anticonvulsants such as skin rashes, hepatotoxicity, and aplastic anemia.[120,166] The hypothesis is supported by a study showing that lymphocytes from children with fetal hydantoin syndrome were more sensitive to oxidative metabolites of phenytoin than lymphocytes from control children.[167] This suggested that they had a deficiency of epoxide hydrolase, a major enzyme that detoxifies arene oxides. In another study of prenatal villous biopsies from fetuses exposed to phenytoin *in utero*, those with epoxide hydrolase levels below 30% of control were later diagnosed with fetal hydantoin syndrome, but those with levels greater than 30% were normal.[163] Interactions of drugs with neurotransmitter receptors and inhibition of histone acetylase activity by valproate have also been proposed as mechanisms for anticonvulsant teratogenicity.[168,169]

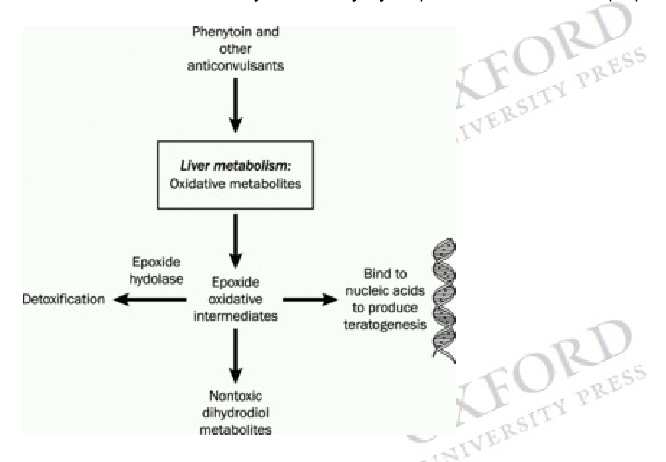




Figure 1–19.
Hepatic oxidative metabolites.

Although valproate was initially considered to have a low risk of teratogenicity, more experience indicates that it actually has a higher risk than older anticonvulsants such as carbamazepine.[68] Valproate also carries a higher risk of neural tube (1%–2%), skeletal, craniofacial, digital, and heart defects than other drugs. Valproate teratogenicity is dose related and may also reduce intelligence in the offspring in the absence of physical defects.[170] The incidence of birth defects is higher when valproate is combined with other anticonvulsants, especially lamotrigine. The teratogenicty of lamotrigine also appears to be dose related, and is higher with doses over 200 mg/d.[171] This is consistent with the hypothesis that the quantity of anticonvulsant metabolites is a determinant of teratogenicity in susceptible fetuses. Based on this information, it is recommended that monotherapy be used if at all possible during pregnancy, and that the dose be as low as possible to control the seizures. If possible, women should also be started on folic acid before they become pregnant, especially if they are on valproate to reduce the incidence of neural tube defects.[164]

Infants and Children

A number of factors cause infants and children to absorb, metabolize, and eliminate drugs differently from adults.[172] As discussed previously, children often metabolize drugs more actively and require higher doses per unit of body weight than adults, and these PK differences contribute to a higher incidence of adverse effects in children, such as skin rashes.[173] In addition, infants sometimes respond differently to drugs in a way that suggests that the targets of drug action may be developmentally regulated. For example, it has been noted that anticonvulsants such as phenobarbital and benzodiazepines are less effective for seizures in newborns than in later life.[174] In experimental models, evidence indicates that the GABA-benzodiazepine receptor responds differently in the neonatal period than later in life by being excitatory rather than inhibitory.[175] At the level of electrophysiology, it has been shown that this is because chloride that passes through the channel associated with the GABA-benzodiazepine receptor moves outward in the neonate in contrast moving inward in older individuals. This difference is caused by the developmental expression of a chloride transporter (NKCC1) in neonates that facilitates the accumulation of chloride inside neurons.[176] In contrast, another chloride-extruding transporter (KCC2) ramps up later in the neonatal period. This leads to high intracellular levels of chloride in the neonatal period, and when the chloride channel opens, chloride moves outward, producing excitation. Bemetanide, an approved diuretic, inhibits the NKCC1 transporter and could be useful for seizure control in neonates. This is an example of a new molecular explanation for a drug effect that differs in neonates

compared to adults.

Elderly Patients

Elderly patients appear to be more susceptible to cognitive side effects and some other adverse effects of drugs than are younger patients.[177] The basis for this increased sensitivity is uncertain, but underlying cognitive problems, changes in PK parameters, and metabolism of drugs by the liver with age and use of multiple drugs, especially sedatives and antipsychotic drugs without proper monitoring, probably contribute (Chapter 7).[178,179] In elderly individuals, the volume of distribution appears to be lower for water-soluble drugs and higher for lipid-soluble agents for albumin-bound drugs, and the free fraction is generally increased. It is important to minimize the number of drugs prescribed, to be aware of the risks of drug interactions, and to determine the minimal therapeutic dosage. One study of drugs used by nursing home residents found that 10% were taking anticonvulsants, and the use of phenobarbital and phenytoin together was relatively common, probably causing some cognitive problems.[180] Of this population, 45% had subtherapeutic concentrations of these drugs and 10 % had levels in the toxic range. This is an area that deserves greater investigation in the future.

Conclusion

The fundamentals of drug therapy are applicable to each of the disease-oriented chapters that follow. Progress in understanding the molecular actions of drugs goes hand in hand with progress in neuroscience and understanding basic disease mechanisms, and this is reflected in the content of these chapters. Modern molecular genetics is producing an explosion of knowledge about the origin of variation in the targets for drugs as well as in the metabolism and side effects. This is leading to improvement in our ability to provide more specific therapies for individual patients.

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Movement Disorders

Chapter: Movement Disorders
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Movement disorders are abnormal, involuntary contractions characterized by either too few movements (hypokinesias) or excessive movements (hyperkinesias). Typically, weakness is not a part of this class of disorders, but a lack of control of the body limits function. Descriptions of movement disorders date back many centuries for some diseases, but scientists continue to try to understand the involved anatomical structures, underlying pathophysiology, and mechanism of action of treatments.

In this chapter, the anatomy of the basal ganglia will be discussed based on neurochemical and structural anatomy. Because the majority of patients with movement disorders have Parkinson's disease (PD), the majority of the chapter will focus on PD, its treatments, and complications of treatments. There have been tremendous advances in therapies, many of which have emerged only since the late 1990s. In addition, nonmotor symptoms of PD and complications of therapy will also be briefly discussed. Other diseases that will be presented include Parkinson-plus syndromes, Huntington's disease, Wilson's disease, essential tremor, ataxia, and dystonia. There are many other movement disorders—such as Gilles de la Tourette's syndrome, tardive dyskinesias, akathisia, restless legs syndrome, myoclonus, and others that are interesting and relevant to patients—but these will not be covered in this chapter.

Neurochemical anatomy of the basal ganglia

The forebrain structures involved in movement include the caudate nucleus, the putamen, globus pallidus (internal and external segments), the subthalamic nucleus, and the substantia nigra. The thalamus is also intimately involved in the anatomic pathway (Figure **2–1**). The general flow of neural impulses is into the caudate and putamen from the cerebral cortex and brainstem, then through the globus pallidus and substantia nigra pars reticulata to the thalamus and other regions of the brain. Although the nucleus accumbens is part of the basal ganglia, its primary role of emotional regulation will not be discussed in detail.

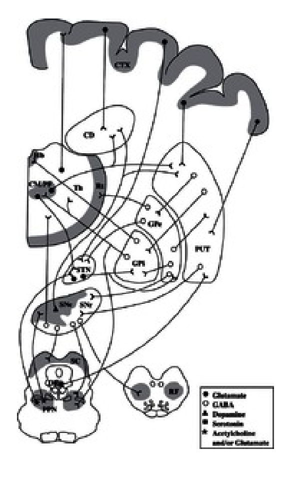






Figure 2–1.
Schematic diagram of major basal ganglia connections in primates. For simplification, some connections have been omitted The main neurotransmitters are indicated by different symbols that label the cell bodies. From Charara, Sidibe, and Smith,[11] Figure 1 with kind permission of Springer Science and Business Media.

One of the difficulties in communication about the basal ganglia is the variation in terms. While anatomists usually subdivide this system according to cytoarchitecture criteria, behavioral neuroscientists tend to use a subdivision based on efferent projections of the Dopamine (DA) system (e.g., mesostriatal and mesolimbic DA systems). As a result, there is presently an abundance of nomenclatures used in the description of the striatal connections with the DA system. This complexity is compounded by the fact that the same terms are often used in rodent and primate research, although it is not always clear that these terms represent analogous areas or subdivisions.[1] In addition to the basal ganglia, other structures are emerging as important in the role of movement initiation and control, including the zona incerta and pedunculopontine area.[2]

There are two circuits that are generally referenced when discussing movement disorders: the direct and the indirect pathways. The direct pathway consists of striatum to globus pallidus pars interna/substantia nigra pars reticulata to thalamus to cortex. The end result of signals through this pathway is disinhibition of the cortex. The anatomic flow through the indirect pathway consists of striatum to globus pallidus pars externa to subthalamic nucleus to globus pallidus pars interna/substantia nigra pars reticulata to thalamus to cortex. The result of the indirect pathway is inhibition of the cortex. Control of movement is thus dependent on the balance between the direct and indirect pathways. Disruption of these circuits manifests as various movement disorders.

Basal Ganglia Structures

The anatomic regions of the brain important in the generation of movement include certain deep forebrain structures, the caudate nucleus and the putamen; their diencephalic projection zones, the globus pallidus and the subthalamic nucleus; the substantia nigra; and the projection pathways from the globus pallidus and the substantia nigra.[3] The general flow of neural impulses is into the caudate nucleus and putamen from the cerebral cortex and brainstem, then through the globus pallidus and substantia nigra pars reticulata to the thalamus and other regions of the brain. Most structures are receptive, but the globus pallidus pars interna is the major outflow structure of the basal ganglia. The afferent, the internal organization and the efferent of each of these regions of the basal ganglia are discussed in turn.

The striatum

The caudate nucleus and the putamen, together with the nucleus accumbens and the olfactory tubercle, have similar histologies and are collectively called the striatum. Anatomically, the striatum is the largest component of the basal ganglia. These nuclei receive major excitatory, glutamatergic inputs from the cerebral cortex. Cortical projections to putamen emanate mainly from the primary motor and sensory cortices, whereas those to the caudate come from the association cortices. The striatum also receives excitatory projections from the intralaminar nuclei of the thalamus. There is a major dopaminergic pathway to the striatum from the substantia nigra pars compacta (SNc) and ventral tegmental area. Lesser serotonergic and noradrenergic projections also emanate from the raphe nuclei and locus ceruleus in the brainstem. The striatum then in turn projects to the pallidum and substantia nigra. The internal segment of the pallidum and the pars reticulata of the substantia nigra are the primary output structures of the basal ganglia. Through these structures, striatal information is projected through the thalamus back to the cerebral cortex, thus closing the so-called cortico-striato-pallido-thalomo-cortical loop.[4]

Internally, the striatum has two major organizational components: the matrix and the striosomes[5] (Figure **2–2**). The striosomes are 1-mm-wide interconnected patches embedded in the matrix. They were first discovered because they have low levels of the enzyme acetylcholinesterase.[6] The matrix and the striosomes have different connections. The matrix compartment receives major projections from upper layers of cerebral cortex (particularly the primary motor, sensory, and associated cortices), the thalamus, the ventral tegmental area, and the dorsal nigra, whereas the striosomes receive afferents from ventral nigra and deep layers of cerebral cortices. A small percentage of striatal neurons are interneurons. These include somatostatin neurons, which are exclusively present in the matrix, and acetylcholine neurons, which occur in both matrix and striosome compartments and which send their processes from one region into the other. All other striatal neurons appear to confine their dendritic processes to the compartment where their soma resides.

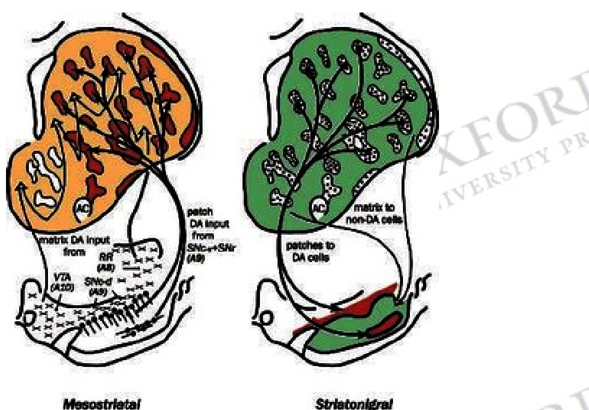




Figure 2–2.
Summary diagram of the compartmental organization of the mesostriatal systems in the rat (left) compared with the compartmental organization of striatonigral systems (B). Dopaminergic afferents to the striatal matrix originate from a dorsal set of midbrain neurons (x) that are located in the ventral tegmental area (A10 cells in the VTA), the dorsal tier of the substantia nigra pars compacta (dorsal A9 cells in the SNc-d), and the retrorubral area (A8 cells in the RR). Dopaminergic afferents to the striatal patches originate from the ventral tier of the substantia nigra pars compacta (ventral A9 cells in the SNc-v), whose dendrites extend ventrally into the substantia nigra pars reticulata, and from the A9 DA cells located in the substantia nigra pars reticulata (SNr). Neurons in the striatal matrix provide inputs to the substantia nigra pars reticulata that avoid the locations of DA cells in both the SNc and the SNr. Neurons in the striatal patches provide inputs to the location of the DA cell bodies and their proximal dendrites in the SNc-v and the SNr. From Gerfen CR, Herkenham M, and Thibauld J. The neostriatal mosaic II: patch-and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *J Neurosci*. 1987;7(12):3932, figure 12. Copyright 1987 by the Society for Neuroscience.

The vast majority of the matrix efferent neurons appear to use γ-aminobutyric acid (GABA) as a neurotransmitter.[5] Many of these GABA neurons contain enkephalin as a colocalized neuromodulator. These neurons appear to project primarily to the lateral portion of the globus pallidus. Other striatal effe rents contain GABA and both substance P and dynorphin. These neurons project to the medial segment of the globus pallidus and the other substantia nigra pars reticulate. Striosomal efferent neurons include both GABA neurons and substance P/dynorphin neurons. The only currently known projection of the striosomes is to pars compacta of the substantia nigra.[7] Both dopamine D2 and muscarinic cholinergic receptor are present in high density in the striatum and GABA/benzodiazepine receptors are also dense in the striatum.

Like all other major brain nuclei, the human striatum is composed of both projection neurons (Golgi type I cells) and local circuits cells or interneurons (Golgi type II cells). However, in contrast to other areas of the brain, the projection neurons greatly outnumber interneurons in the striatum.[8] Striatal neurons fall into two broad categories: (1) those with spiny dendrites, smooth nuclear envelope, medium-sized oval or round cell body, and a long axon, which are considered the striatal projection neurons, and (2) those with smooth dendrites, strongly indented nuclear envelope, medium-sized to large-sized pleomorphic cell body, and a short axon, which represent the striatal interneurons.[8] Virtually all medium spiny neurons use GABA as their main neurotransmitter but also coexpress a number of peptides including substance P, enkephalin, dynorphin, and neurotensin.[8]

The striatal interneurons can be grouped into two broad categories according to their cell diameters: (1) the medium aspiny interneurons, and (2) the giant aspiny interneurons.[9] The medium interneurons have been further divided into three subcategories based on their neurochemical content. Not all of these substances are found in every neuron, but are contained in subsets of projection neurons. The first type displays intense immunoreactivity for GABA and/or its synthesizing enzyme glutamic acid decarboxylase. The second type displays immunoreactivity for somatostatin or neuropeptide Y. A third type expresses calretinin. The giant interneurons display immunoreactivity for choline acetyltransferase, the enzyme that synthesizes acetylcholine, and are thus considered the cholinergic neurons of the striatum.[8]

The lateral globus pallidus and subthalamic nucleus

The lateral globus pallidus consists of large, mulitpolar GABAergic neurons. The vast majority of these neurons are efferent neurons although apparently there are some interneurons. The lateral pallidal neurons send their axons to the subthalamic nucleus (STN), which also receives projections from the cerebral cortex, particularly the motor regions. The cortical pathway is excitatory and presumably glutamatergic. The neurotransmitter used by STN neurons is also thought to be excitatory and glutamatergic. Subthalamic projections go back to the lateral pallidum and striatum and out to the medial segment of the globus pallidus and the pars reticulata of the substantia nigra. Thus, information from the GABA/enkephalin striatal matrix neurons goes to the lateral globus pallidus and is then relayed via the STN to the medial segment of the globus pallidus and the substantia nigra pars reticulata. Here the information is processed along with that of the matrix substance P/dynorphin direct projections to nigra and medial pallidum.

The medial globus pallidus and substantia nigra pars reticulata

The medial globus pallidus and substantia nigra pars reticulata consist of large GABAergic neurons similar to those in the lateral globus pallidus. The medial globus pallidus appears to receive the majority of its striatal protections from the putamen. Its efferents project to the pars oralis of the ventral lateral thalamic nucleus, which in turn projects to the supplementary motor cortex.[10] This pathway joining the putamen, medial globus pallidus, thalamus, and supplementary motor cortex may be the primary route by which the basal ganglia influence spontaneous movements.

The substantia nigra pars reticulata receives the majority of its striatal afferents from the caudate, and it has a number of important projections. One is a projection to the dopaminergic pars compacta neurons, which thus completes a nigral-striatal-nigral feedback loop. Another projection is to the ventral anterior and medial dorsal nuclei of the thalamus, which in turn projects to the prefrontal cortex. This pathway joining the caudate, pars reticulata, thalamus, and prefrontal cortex is thought mediate the behavioral disorders seen in basal ganglia disease. A third major pathway goes from the pars reticulata to the superior colliuculus. This pathway subserves an important basal ganglia influence on eye movements.[3] Pars reticulata projections to the reticular formation may mediate basal ganglia effects on tone (muscle resistance to passive stretch).

Striatal Afferents

The cerebral cortex

The cerebral cortex sends large projections to the caudate and putamen. The neurotransmitter of the cortical pathways is thought to be the excitatory amino acid glutamate. Motor and sensory cortex project principally to the extrastriosomal matrix of the putamen. Association and cingulate cortices project to the matrix of the caudate. The posterior parietal cortex projects to the dorsolateral caudate, the dorsolateral prefrontal cortex to the central caudate, and the anterior cingulate cortex to the ventromedial caudate.

The striosomes receive projections from the medial prefrontal cortex, insulotemporal cortex, and basolateral amygdala. They also receive minor projections from deep layers of the other cortical regions. The implication of these differential projections to striosome and matrix is that there may be distinct circuits for the basal ganglia modulation of limbic and motorsensory tasks.

Thalamic projection to the striatum

The centromedian and parafascicular nuclei of the thalamus provide another glutamatergic input to the striatum. The projections innervate primarily the extrastriosomal matrix.[11] The purpose of this major, well-organized projection is yet unknown, but the thalamus may provide the striatum with behaviorally significant sensory events.[12]

The substantia nigra pars compacta

One of the best-studied projections to the striatum is the dopaminergic pathway from the substantia nigra pars compacta. Similar to other areas, the projections are topographically organized. Most studies have shown that tyrosine hydroxylase and dopamine-containing fibers terminate relatively homogenously throughout the rat striatum.[11]

Brainstem projections to the striatum

The serotonergic cells in the raphe nuclei send projections to the substantia nigra, the striatum, and the pallidum. There are also projections to the striatum from the subthalamic nucleus, pedunculopontine nucleus, and locus ceruleus. The role of these pathways in modulating striatal outflow is unclear.[11] Serotonergic dysfunction, however, has been linked to depression in patients with Parkinson's disease.[13] This pathway also may be involved in autonomic dysfunction as well as sleep disorders in various diseases.

Clinical Implications

The circuitry of the basal ganglia is quite complex, and as our knowledge increases, the apparent complexity increases as well. Nevertheless, some generalizations can be made about the system that allows one to interpret the clinical symptomatology in terms of neuronal circuitry.

Inclusive of the indirect and the direct pathways, two major circuits seem to be modulated by the striatum.[4,14] The first is the limbic circuit, which is relatively self-contained and includes the medial prefrontal and insulotemporal cortices, the basolateral amygdala, the striosomes, and the densocellular area of the substantia pars compacta. The second circuit probably modulates motor and sensory function, because it includes association, motor and sensory cortices, matrix, pallidum, subthalamic nucleus, substantia nigra pars reticulata, thalamus, superior colliculis, and the brainstem.

This latter, larger circuit can be thought of as two separate but interconnecting circuits. The first pathway is from cortex to matrix to medial pallidum and pars reticulata and then to thalamus and cortex. It is probably modulated by dopaminergic input from the substantia nigra in an excitatory fashion (i.e., dopamine normally excites or stimulates this circuit). The second pathway is from cortex to matrix lateral pallidum to subthalamic nucleus to medial pallidum/pars reticulata and then to thalamus and cortex. This circuit is inhibited by dopaminergic inputs.

Loss of dopamine to the striatum, such as in Parkinson's disease, therefore results in excessive suppression of spontaneous movements. In the striatum, loss of specific subgroups of neurons may lead to quite different clinical abnormalities. Loss of matrix inhibitory inputs to lateral pallidum should result in chorea, as would a subthalamic nucleus lesion, whereas loss of matrix projections to medial pallidum or pars reticulata might result in akinesia or dystonia.

As techniques such as functional magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and other technologies are developed and used in patients with pathology, the understanding of basal ganglia anatomy and its diseases is improved. Future studies of basal ganglia pathophysiology will move microscopic in vitro techniques to animal and human in vivo measurements. Ongoing improvements in understanding of the neurochemical basis of anatomy will continue to address the relationship between clinical symptomatology and selective striatal pathology.

Parkinson's disease

Clinical Manifestations

Parkinson's disease is a progressive neurodegenerative condition with motor symptoms characterized by the asymmetric onset of rest tremor, bradykinesia, and rigidity. Eventually, most patients also develop balance and gait abnormalities. There is a notable lack of psychotic features, falls, and cortical dementia early in the disease process. On examination, there is typically slowing of rapid alternating movements of the hands and feet. On passive movement, there is rigidity that can be augmented with movement of the opposite limb. The characteristic gait abnormalities of PD include slow shuffling steps, stooped posture, and difficulty with turns. Postural instability with antero- or retropulsion resulting in falls is often seen later in the disease course.

The diagnosis of probable PD is based on the demonstration of three of four cardinal features including asymmetrical onset, bradykinesia, rigidity, and tremor.[15] In addition, there are pathological correlates to confirm the diagnosis that are used for clinical trials.[16] One of the strongest supporting features includes a clear response to dopaminergic therapy, particularly to levodopa. Exclusion criteria for the diagnosis include exposure to medications known to cause Parkinsonism (predominately neuroleptics and antiemetics), cerebellar deficits, corticospinal tract signs, and occulomotor deficits other than a slight limitation of upward gaze. Early autonomic impairment or dementia also suggest an alternative diagnosis.[17] Although there are many causes of Parkinsonism, PD is the most common cause and will be the primary focus of this chapter.

Most reported estimates of age-adjusted frequency of PD vary from 9.7 to 13.9/100,000 person-years.[18–21] One estimate of the lifetime risk of developing PD was 2% for men and 1.3% for women.[22] The typical age of onset of PD is in the sixth decade, but 5%–10% of cases are "young onset" with symptoms starting under 45 years of age. The disease progresses over time with substantial morbidity associated with the disease and its complications.

Neurotransmitter and Receptor Changes

Multiple neurotransmitters are affected in patients with PD. The pathologic changes in PD corresponding to the motor dysfunction seen in PD patients is the loss of the dopamine producing cells of the substantia nigra and, to a lesser extent, of the ventral tegmental area. The pigmented cells of the substantia nigra are more severely affected than the nonpigmented cells.[23]

Of the described dopamine receptors, D2 receptors are found in the caudate and putamen and are thought to be the main receptors involved in control of the motor system. The D2 receptor is also the site of action of most of the dopamine agonist action.[24] Since D3 receptors have the highest concentration in the mesolimbic system, it is most likely involved in control of behavior and mood. However, in PD, it may be a loss of D3 receptors that determines the response to medications.[25]

There are numerous nonmotor features of PD, which are likely caused by dysfunction of other neurotransmitters (Table 2–1). The autonomic dysfunction associated with PD is likely cause by neuronal loss in the locus ceruleus and consequent loss of norepinephrine terminals in the forebrain. Norepinephrine may also be involved in the "freezing" of gait.[26] Serotonin depletion has been found in a number of depressed Parkinsonian patients' brains, which may explain the high incidence of depression in Parkinsonian patients.[27] Tremor is responsive to acetylcholine blockade and the acetylcholine system may account for the increased rates of dementia in patients with PD.

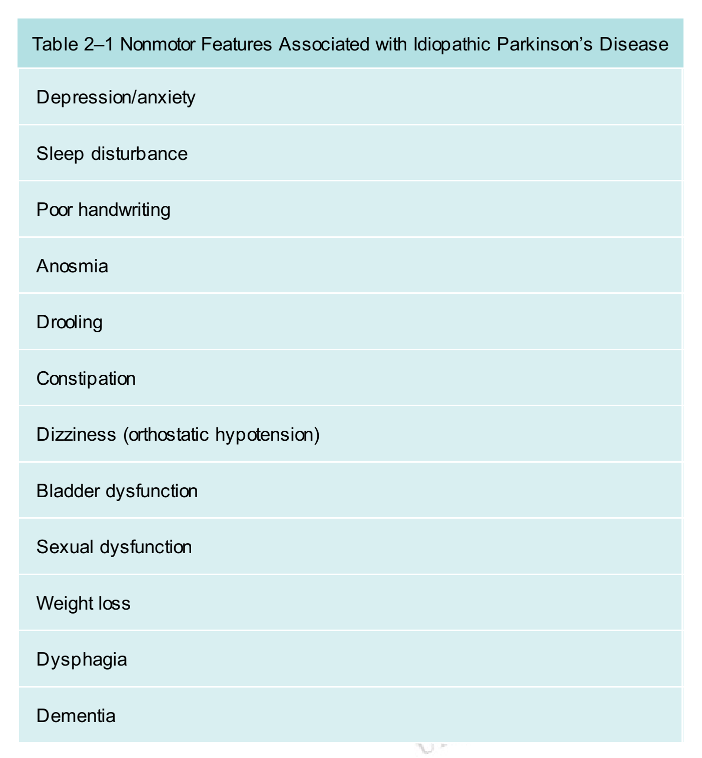


Table 2–1 Nonmotor Features Associated with Idiopathic Parkinson's Disease
Depression/anxiety
Sleep disturbance
Poor handwriting
Anosmia
Drooling
Constipation
Dizziness (orthostatic hypotension)
Bladder dysfunction
Sexual dysfunction
Weight loss
Dysphagia
Dementia



Neuroimaging has provided insight into the location of pathology in PD. Routine imaging can evaluate for structural changes that may cause other forms of Parkinsonism, such as normal pressure hydrocephalus, ischemic lesions, or basal ganglia changes related to neurotoxins. However, other than global atrophy, routine imaging is typically normal. Advances in MRI imaging with pulse sequences can show structural changes in the SNc even in the earliest cases of symptomatic disease.[28] Threedimensional 18–fluorodopa positron emission tomography (FDOPA-PET) studies demonstrate the loss of FDOPA uptake in both the contralateral and ipsilateral putamen as well as in the contralateral caudate in early hemi-PD patients. There is an average 12% annual decline in baseline putamen FDOPA values in PD patients.[29] There are suggestions that radiotracer imaging techniques may be useful, but currently there are too many uncertainties to use imaging techniques as an established surrogate marker.[30]

Selective Vulnerability

The primary pathology is located in the SNc, the main source of dopamine in the motor system. Neuron degeneration also involves other systems, including mesocortical dopaminergic cells, noradrenergic (locus ceruleus), serotonergic (dorsal raphe nuclei), cholinergic (nucleus basalis of Meynert), histaminergic, and peptidergic systems.[31] Intranuclear inclusions of alpha-synuclein form in diseased neurons called Lewy bodies.[32] There are typically pathological changes seen prior to the onset of clinical symptoms and Braak and colleagues have proposed a staging system to delineate pathological changes (Figure **2–3**).[33] During presymptomatic stages 1–2, Lewy body pathology is confined to the medulla oblongata, pontine tegmentum, olfactory bulb, and anterior olfactory nucleus. In stages 3–4, the substantia nigra, the midbrain, and forebrain are affected. At this point, most individuals cross the threshold to the symptomatic phase of Parkinson's disease. In stages 5–6, the process enters the mature neocortex, and the full features of Parkinson's disease are manifest.

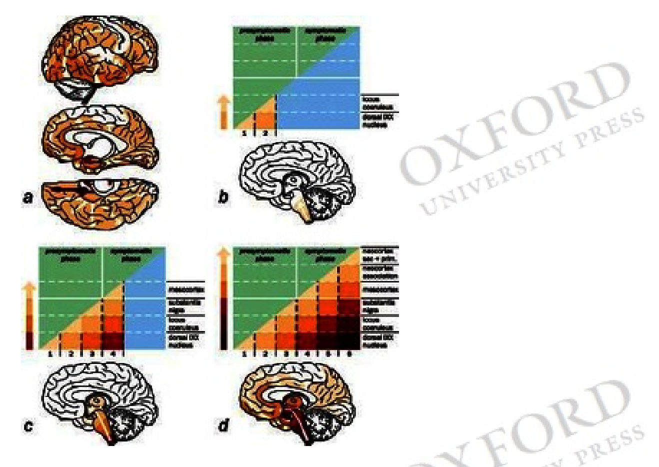




Figure 2–3.
Schematic diagrams showing the gradual ascent of the pathological process underlying IPD. (B) During the presymptomatic stages 1 and 2, the PD-related inclusion body pathology is confined to the medulla oblongata and olfactory bulb. (C) In stages 3 and 4, the substantia nigra and other nuclear grays of the midbrain and basal forebrain become the focus of initially subtle and, then, severe changes. The illness most probably reaches its symptomatic phase in many individuals. (D) In the final stages 5 and 6, the lesions encroach upon the cerebral cortex, so that PD manifests itself in all of its aspects: somatomotor dysfunctions are supplemented by increasing deterioration of cortically-controlled intellectual capabilities (d). From Braak and colleagues.[33] With kind permission of Springer Science and Business Media.

The cause of PD is not known, although multiple factors that may increase the risk of developing PD have been proposed including aging, genetic predispositions, environmental and occupational exposures, and life style.[34–40] In a study of twin siblings, monozygotic–dizygotic concordance rates were indistinguishable, implying a strong probability of an environmental influence.[41]

Genetic influence

There are four confirmed genes linked to early-onset PD (α-synuclein, parkin, DJ-1, and PINK1), but only mutations in the leucine-rich repeat kinase 2 gene (LRRK2) have

been identified in families with autosomal dominant late-onset PD.[42,43] A family history of Parkinson's disease exists in approximately 15% of patients.[44] Abnormalities in α-synuclein and parkin genes have been shown to contribute to Parkinson's disease. Alpha-synuclein is a ubiquitous neuronal protein of unknown function that may have a role in synaptic vesicle transport or recycling. The discovery that α-synuclein mutations could cause PD led quickly to the discovery that it was the principal component of Lewy bodies.[45] The PARK 1 genetic form is an autosomal dominant form due to an α-synuclein mutation. The PARK 2 genetic form is related to a mutation in parkin, an ubiquitin ligase. It is inherited in an autosomal recessive fashion. Parkin mutation is the single most common genetic cause of PD, and in one European study was found to be present in 40% of cases with onset before age 40.[46] There are at least 12 different genetic loci involved in inherited Parkinson's disease, but most have been described in single-family studies. By understanding the cellular impact of these genetic changes, we may be better able to characterize the pathological cascade that results in Parkinson's disease. Although there is evidence of genetic influence, environmental factors appear to have more weight in causing PD, although the combination is likely needed to precipitate the disease.[47,48]

Environmental exposures

There are multiple studies suggesting an association between environmental exposures and an increased risk of PD. Potential toxins include pesticides, herbicides, insecticides, and various heavy metals.[36,49–58] Various lifestyle and behavioral risk factors have been reported to have an association with PD. There may be an association between lower alcohol intake and reduced incidence of PD.[64,65] Some of these risk factors include lifetime exposure to well water, head trauma, endocrine conditions, depression, level of education, dietary influence, rural living, calcium and amalgam, and infections.[63] Several studies have associated an increased risk of PD with vocations including farming, carpentry, cleaning, metallurgy, sales, specific crafts, clergy and religious work, teaching, and medical work.[67] However, other studies contradict these findings and do not support an association with occupation.[67–71] Because there are studies that dispute the associations of lifestyle and exposures, no clear conclusion can be made at this time.[59–62] There are multiple neurodegenerative diseases that may have an association with occupation.[72]

One of the best models of a toxic exposure came from the accidental exposure to 1–methyl-4–phenyl-1,2,3,6–tetrahydropyridine (MPTP) by drug abusers as a substitute for meperidine who subsequently acutely developed a Parkinsonian syndrome. It is now used as a Parkinson-inducing agent in experimental animals. MPTP is converted to MPP+ by monoamine oxidases (MAO) type B and is taken up by the dopamine transport system and binds to neuromelenin, the most likely mechanism of its toxicity. There are immediate and longterm effects, although there is no formation of Lewy bodies. Neuropathological study of three patients with MPTP-induced Parkinsonism revealed moderate to severe depletion of pigmented nerve cells in the SNc. There were findings consistent with active, ongoing nerve cell loss, suggesting that a time-limited insult to the nigrostriatal system can set in motion a self-perpetuating process of neurodegeneration.[73]

There are a few exposures that may reduce the risk of developing PD, including caffeine and smoking. Caffeine has consistently been associated with a reduced risk of developing PD. A systematic review of the studies done between 1968 and 2001 on the association between caffeine intake and risk of PD demonstrated a pooled relative risk (RR) of 0.69 (95% confidence interval [CI] 0.59–0.80) for coffee drinkers compared with non-coffee drinkers.[66] Smoking and a reduced risk of PD was first reported in 1959.[74] A review of prospective studies up to 1997 found seven prospective studies.[75] The pooled RR for "ever" smokers (including current and former) compared to never smokers was 0.51 (95% CI 0.43–0.61), but the included studies had many limitations and further studies are needed, particularly in women.

Rational for Therapy of Motor Symptoms

Levodopa

An extensive number of medications are available for the symptomatic treatment of Parkinson's disease. Levodopa was introduced as a PD therapy in the 1960s, and remains the most effective therapy for motor symptoms.[76] It alleviates all the cardinal motor symptoms of PD, including bradykinesia. Levodopa is a large neutral amino acid, which is absorbed in the gut and transported across the blood brain barrier (BBB) by a neutral amino acid transporter. It is converted to dopamine intraneuronally and in other places where amino acid decarboxylase activity is present. As a result, dietary protein can interfere with its absorption.[77] Levodopa administered by mouth is almost completely absorbed from the gut. Peripherally, levodopa is mainly metabolized by the enzymes aromatic amino acid decarboxylase (AAAD) and catechol-O-methyltransferase (COMT) (Figure **2–4**). Less than 5% of an oral dose of levodopa (in isolation) crosses the BBB. To improve the central transport, levodopa is combined with carbidopa (an AAAD inhibitor) to decrease the peripheral metabolism of the levodopa. The plasma half-life of levodopa is about 50 minutes, without carbidopa. When carbidopa is added, the half-life is increased to about 1.5 hours.

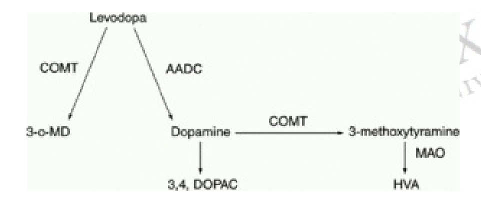


Figure 2–4.
Levodopa is converted into dopamine after it crosses the BBB. Dopamine is then degraded into two main metabolites.

During initial therapy with levodopa, the presynaptic terminals are still able to store dopamine. As a result, the effects of the levodopa are smooth throughout the dosing period. As the disease progresses and the lack of storage capacity in the presynaptic terminals becomes clinically significant, the patient experiences "wearing off," in which the effects of levodopa do not last between doses.

Carbidopa/levodopa is available in a variety of formulations (Table 2–2). Controlled-release (CR) formulations are not as well absorbed and the bioavailability is 20%–30% lower than standard preparations. A comparison of the twoformulations found a small improvement in the activities of daily living score in the CR group.[78] There does not appear to be a difference in motor complications between immediate and sustained release carbidopa/levodopa formulations. There are no clear benefits of immediate versus sustained release formulations, but later in the disease, the response to the continuous release may not be as predictable.[79] Carbidopa/ levodopa is also available in an orally disintegrating tablet, which does not change the time of onset, but it is equally effective as conventional formulations. It is particularly useful in patients with swallowing difficulties.[80]

Table 2–2 Formulations of Carbidopa/Levodopa			
Formulation	**Available Doses**	**Onset of Action**	**Effect of Medications**
Carbidopa/levodopa IR	10/100, 25/100, 25/250	20–40 min	2–6 h
Carbidopa/levodopa CR	25/100, 50/200	40–60 min	4–6 h
Carbidopa/levodopa orally disintegrating tablets	10/100, 25/100, 25/250	20–40 min	2–6 h

The immediate benefit of levodopa therapy can be seen even in low dosages. There is a clear dose response curve (Figure **2–5**). There have been suggestions that the "cost" of therapy is faster progression of disease. However, recent evidence suggests that levodopa may actually be protective against faster disease progression.[81] An alternative theory as to the lack of worsening after levodopa was withdrawn in that study may be underlying receptor changes that persist longer than four weeks.

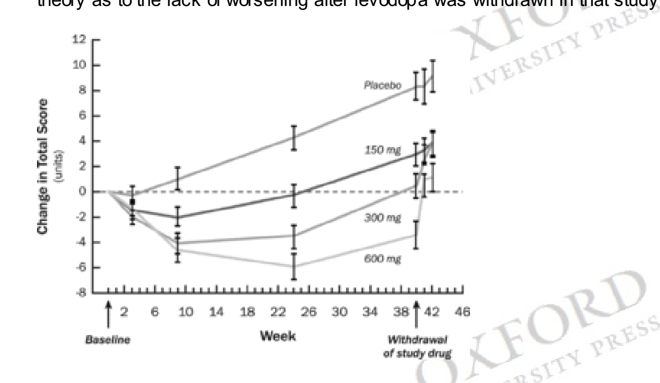


Figure 2–5.
Changes in total scores on the UPDRS from baseline. Improvement in Parkinsonism is represented by lower scores and worsening by higher scores. Negative scores on the curves indicate improvement from baseline. The bars indicate the standard error. From Parkinson Study Group.[81] Copyright 2004 Massachusetts Medical Society.

The initial adverse effects of levodopa are due to the conversion to dopamine outside the brain, resulting in accumulation of dopamine in the blood stream and stimulating the dopamine receptors in the gastrointestinal system. Nausea and vomiting can be seen with medication initiation and can be reduced or avoided with a slow titration. Carbidopa is available separately as adjunct therapy with carbidopa/levodopa in those patients that are having significant difficulties with nausea and vomiting.

Dystonia is a condition of abnormal posturing that can result in pain and functional impairment. Dystonia in PD typically consists of a painful involuntary cramping or twisting of a limb, classically the foot or leg. The most common time of day for the dystonias to occur is early in the morning when dopamine levels are lowest, but dystonia can also occur during the night or during the day when medications are wearing off.

Over time, the postsynaptic dopamine receptors are down regulated resulting in an abnormal postsynaptic response.[82,83] Dyskinesias are abnormal, involuntary flowing movements that likely result from an inappropriate response to levodopa administration. Dyskinesias are a side effect of long-term use of levodopa observed in the majority of patients with Parkinson's disease who have been treated for 5–10 years with levodopa.[84] Dyskinesias are typically related to peak levodopa plasma levels or to a relative change in the plasma levodopa level.[85] As the disease progresses, the dose required for symptomatic control approaches that which induces intolerable dyskinesias, thus narrowing the therapeutic window and limiting medical therapy. Dyskinesias are one of the primary limitations to medical therapy, a principal motive for considering surgical intervention, and can impact quality of life.[86,87] Therapies for decreasing dyskinesias include lowering the amount of levodopa per dose, adding a COMT or monoamine oxidase type B (MAO-B) inhibitor, or adding amantadine.

In addition to dyskinesias, there are other motor complications of PD that may occur as part of the progression of the disease, particularly if levodopa is used early in the course of disease. Some of the complications of medical therapy may also be a sign of DA understimulation. The complications include wearing off, gait freezing, and "on/off" phenomenon. In wearing off, the clinical effect of medication does not last between doses. Gait freezing presents with a sudden stopping of gait or progressively smaller stride length until patients come to a stop. "On" and "off" phenomenon occur much as the name implies; patients turn off as if someone turned off a light switch and suddenly become slow, stiff, and tremulous. When the episode resolves, a switch is then turned "on" again and patients become more mobile, fluid, and less tremulous.

Dopamine agonists

These agents directly stimulate the postsynaptic dopamine receptors. Although as a class they are not as effective as levodopa on the cardinal symptoms of Parkinson's disease, they also do not have the same degree of motor complications.[88,89] They can be used as monotherapy or in lower doses as adjunctive therapy. A number of dopamine agonists are available (Table 2–3).

Table 2–3 Dopamine Agonists Available (Based on Data from Kvernmo[24])				
Dopamine Agonist	**Class**	**Range of Therapeutic Dosage**	**Half-life**	**Principle Binding Sites D2 Subreceptors**
Apomorphine	Nonergot	2–20 mg/d	40 min	D4>D2, D3, D5
Bromocriptine	Ergot	7.5–30 mg/d	6 h	D2, D3>D4
Cabergoline	Ergot	2–5 mg/d	65+ h	D2, D3>D4
Pergolide	Ergot	1.5–12 mg/d	12–27 h	D2, D3>D4
Pramipexole	Nonergot	1–4.5 mg/d	8–12 h	D3>D2>D4
Ropinirole	Nonergot	3–24 mg/d	6 h	D3>D2>D4

Clinical trials of several of the agonists (e.g., pergolide, pramipexole, ropinirole) have shown their ability to delay motor complications when used as monotherapy early in the disease. There is no conclusive evidence that the dopamine agonists are neuroprotective, but changes on investigational imaging techniques have been observed.[90,91] Whether to initiate therapy and which dopamine agonist to choose depends on multiple factors including age of the patient, the speed of titration, and results from prior medications. For patients with significant swallowing difficulties, non-oral forms of agonists are available in injectable form (apomorphine) and a transdermal patch (rotigotine).[92]

Drowsiness is a common side effect of dopamine agonists, but an uncommon but potentially serious side effect is the phenomenon of "sleep attacks." These episodes of sudden onset of sleep have been reported in patients without warning signs.[93,94] They are more common when increasing doses or switching regimens. It is important to advise patients of this possibility as they may choose to limit their driving during medication transition times. Agonists tend to produce more edema and psychosis than levodopa, which can be particularly troublesome in the elderly or demented Parkinson's patient.

Pulmonary and retroperitoneal fibrosis are rare reported side effects related to the ergotderived dopamine agonists.[95,96] This is felt to be related to its 5HT-2B antagonism versus the 5HT-2B agonism of the other ergot dopamine agonists.[97] It is unclear if the risk increases with dose of medication and duration of use.[98] In most cases, the effects reverse after withdrawal of the ergot dopamine agonist.

Patients taking dopamine agonists are also at higher risk for impulsive and compulsive behaviors such as pathological gambling and shopping. They have also been associated with hypersexuality and punding (an intense fascination with a repetitive activity).[99] All of the dopamine agonists have been implicated.[100]

The receptor activation profile of apomorphine most closely matches that of levodopa, and it can provide a quality of symptomatic benefit that is equivalent to that of levodopa. The available clinical studies indicate that apomorphine is effective in providing prompt and consistent rescue from "off" episodes in patients with PD.[101] It is not orally available, and must be administered via a subcutaneous injection. Trimethobenzamide, an antiemetic, should be started three days prior to initiation of therapy with apomorphine because of the prominent initial emetic effects. After at least 8 weeks of therapy, trimethobenzamide can be tapered and discontinued. Apomorphine should not be given with 5HT3 antagonists such as ondansetron, and it should be used with caution in patients taking antihypertensive medications and vasodilators.

Pramipexole is effective as monotherapy or adjunct therapy for Parkinson's disease.[102,103] Although the SPECT scans were consistent with higher dopamine binding capacity in the pramipexole group compared to the levodopa group after 4 years, the Unified Parkinson's Disease Rating Scale "off" scores in these two groups were equal.[91,104]

Ropinirole is also effective as monotherapy or adjunct therapy for the treatment of patients with Parkinson's disease.[89,105] A 5–year levodopa-controlled randomized prospective trial in de-novo PD patients revealed that patients had fewer dyskinesias in the ropinerole group.[89] A 2–year randomized double-blind prospective trial of ropinirole versus levodopa demonstrated a decrease in the rate of progression of decline of putaminal 18–F-dopa PET uptake in the ropinirole group as compared to the levodopa group.[90]

Other dopamine agonists are also used, but to a lesser extent because of lower potency compared to ropinirole and pramipexole. Bromocriptine is a protein-bound, rapidly absorbed, and hepatically cleared dopamine agonist. Although it is more effective than placebo, it is the weakest of the dopamine agonists. Pergolide is highly protein bound. It is effective in the treatment of Parkinson's disease, but no longer available in the United States due to the complication of cardiac valve fibrosis.[106] Cabergoline is a long-acting ergot dopamine agonist shown to be safe and effective as monotherapy and add-on therapy to levodopa. Parkinson's disease patients who had cabergoline added to their regimen were able to reduce their levodopa needs by 175 mg/day compared to 25 mg/day in the placebo group. In addition, patients had significant reductions in "off" time.[107]

Comt inhibitors

Inhibition of COMT prevents conversion of levodopa to 3–O-methyldopa in the periphery, thus increasing the levodopa available for transport into the brain. Entacapone is the primary COMT inhibitor used and is dosed at 200 mg with each levodopa dose. Coadministration of entacapone with levodopa improves the disability and quality of life in patients with PD.[108] Parkinson's disease patients with and without motor fluctuations benefited from the addition of entacapone to their levodopa treatment. They had improved activities of daily living (ADL) scores and a reduced levodopa requirement of 40 mg. "on" time was improved by 1 hour during the day.[109] The most common side effects are change in the color of urine, insomnia, dizziness, nausea, and hallucinations. Most pro-dopaminergic side effects occur shortly after initiation of entacapone and lessen as levodopa doses are decreased.[110] A combination of carbidopa/levodopa and entacapone in a single pill is also available. It has a similar side effect profile to each agent when used alone.

Tolcapone is another COMT inhibitor dosed at 100 or 200 mg three times a day. In patients with fluctuating Parkinson's disease, tolcapone increased "on" time by 2 hours per day. Patients may have their levodopa dose reduced by up to 200 mg.[111] The most commonly described side effects are nausea, dyskinesia, anorexia, sleep disorders, diarrhea, and vomiting. All except for the diarrhea were felt to be related to concomitant levodopa treatment.[112] Three cases of acute fulminate hepatic necrosis with death have been reported and led to the recommendation of monitoring liver function prior to and while taking tolcapone. If either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become elevated greater than two times normal, the drug should be discontinued.

Monoamine oxidase type b inhibitors

Monoamine oxidase type B acts in the brain to degrade dopamine and MAO-B inhibitors are therefore useful in the treatment of PD. Selegiline and rasagiline are selective, irreversible inhibitors that provide mild symptomatic relief of Parkinson's disease symptoms.[113,114] Theoretically, combining these medications with tricyclic antidepressants or selective serotonin re-uptake inhibitors (SSRIs) increases the risk of serotonin syndrome associated with life-threatening high blood pressure. However, tyramine challenge with rasagiline has not produced evidence that this syndrome will develop.[115]

Selegiline offers mild symptomatic benefit, primarily for patients with early disease. It is dosed at 5 mg twice a day. Side effects include insomnia, hallucinations, and orthostatic hypotension. Selegiline was investigated as a potential neuroprotective trial in PD, the

DATATOP trial. The results suggested a mild symptomatic benefit, but there was not likely an impact on the course of PD. In addition, the time required to wash out symptomatic effects was greater than the washout period allotted in the trial, thus making further interpretations difficult. Selegiline has a metamphetamine metabolite, which is a likely culprit contributing to insomnia. A newer delivery system for selegiline bypasses first pass metabolism and, therefore, there are insignificant levels of metamphetamine and may be a better alternative in patients with significant insomnia.

Rasagiline improves the functioning of patients on the medication and showed potential as a neuroprotective agent in a randomized, delayed start study[116] (Figure **2–6**). Rasagiline produces an improvement in motor fluctuations and Parkinson's disease symptoms in levodopa-treated patients. The only adverse events significantly more common with rasagiline than with the placebo were balance difficulties, anorexia, vomiting, and weight loss.[117] The frequency of adverse effects in patients using rasagiline as adjunctive therapy with levodopa was similar to those in patients taking the placebo.[118] At dosages greater than 2 mg per day, rasagiline loses its selectivity for MAO-B and inhibits MAO-A.



Figure 2–6.

Mean (±1 SE) change in the UPDRS score for each group. (A) Total unadjusted UPDRS score by visit for each treatment group. (B) Unadjusted UPDRS score by visit for each treatment group who completed 52 weeks of treatment without starting additional therapy. From *Arch Neurol*. 2004;61:564.[114] Copyright 2004, American Medical Association. All rights reserved.

Other pharmacotherapies for parkinsons disease

Amantadine is an anti-influenza treatment that was serendipitously found to improve Parkinsonism. The exact mechanism of action is unknown. It is typically used as monotherapy or adjunct therapy early in the disease and may be useful in decreasing dyskinesias in later stages of PD.[119] It is associated with confusion and hallucinations. There can be confusion if the drug is tapered up or down too quickly. In addition, patients often experience livido reticularis and lower extremity edema while taking therapeutic doses.

Anticholinergic medications have been used for PD since the mid-1800s. Triehxyphenidyl and benztropine are most commonly used for troublesome tremor. Due to their long history of use, few rigorous studies of anticholinergic medications have been completed.[120] However, for a minority of patients with refractory, troublesome tremors, these medications may be used. Many clinicians hesitate due to the cognitive side effects and preliminary reports that Alzheimer's pathology may be increased with chronic use of anticholinergic medications.[121]

Surgical Treatment

Surgery for PD was the main treatment for PD until the development of levodopa. Due to the limitations of medical therapy, in the 1990s there was a re-emergence of investigations and use of surgeries for PD. Although ablative procedures may still be rarely used, placement of deep brain stimulation (DBS) electrodes in the STN is the main surgical treatment. This procedure and device improves motor scores, ADL scores, dyskinesias, and permits a decrease levodopa requirements.[122] In a 6–month study of patients with severe motor complications of Parkinson's disease, neurostimulation of the STN was more effective than medical management alone.[123] Subthalamic nucleus stimulation has good outcomes with relatively low risk and little cost burden in PD patients with levodopa-induced motor complications.[124,125]

Other surgical therapies are used, such as bilateral and unilateral DBS of the Globus Pallidus Interna (GPi), predominately when STN cannot be accessed or there is prominent dystonia.[122] An additional study of unilateral GPi stimulation revealed worsening of UPDRS motor fluctuations, and increased medication usage.[126] Cell-based therapies (including autoadrenal transplantation, xenotransplantation, fetal cell transplantation, and stem-cell therapies), neurotrophic factor infusion, and gene transfer procedures for Parkinson's disease are in their infancy. Although there is hope, procedures to date have not shown efficacy, and there can be associated morbidity due to the procedures.[127]

Treatment Approaches

Treatment decisions are based on several factors including age, severity of illness, stage of disease, complications of therapy, and presence of dementia. Initially, the severity of the disease is the most important issue. If the symptoms are mild, the patient may chose to wait to initiate treatment. There are no agents that definitively slow the progression of PD, although clinical trials of available medications and investigational medications are ongoing. The MAO-B inhibitors have suggested possible neuroprotective effects, but so have the dopamine agonists and levodopa.[79,81,128]

When symptoms progress to require significant symptomatic therapy, levodopa or dopamine agonists are typically considered first. Levodopa is the most potent of the anti-Parkinsonian medications with a higher risk of motor complications. Dopamine agonists are not as potent and do not have as significant motor complications but have other potential side effects. In most cases, a younger patient may be started on a dopamine agonist or a dopamine agonist with a small amount of levodopa. If the side-effect profile of the dopamine agonist makes it a less desirable option, levodopa may be an initial choice, regardless of age. In patients with cognitive difficulties, levodopa causes fewer cognitive side effects.[79]

As PD progresses, medication doses are increased and dosing intervals are narrowed in an attempt to smooth out the effects of the levodopa. Titration schedules are adjusted to optimize "on" time of the patient. Typically, medications such as dopamine agonists, COMT inhibitors, and MAO-B inhibitors are added to help to stabilize the effects of the levodopa. Inevitably, dyskinesias develop with long-term levodopa therapy. Decreasing the level of levodopa the patient is receiving may offer some improvement, but adding amantadine may reduce dyskinesias without worsening Parkinsonism. Surgery is also typically considered at the point when patients fluctuate between "on" with dyskinesias and "off" states.[129]

PD-Associated Symptoms and Treatment Options

With better understanding of the dopamine system and its impact on the motor system, the other neurotransmitters and nonmotor features of PD have been studied further.[31,130] The widespread degeneration in the brain of PD patients influences special senses, contributes to autonomic changes, and can lead to cognitive and emotional difficulties. Smell and vision are frequently affected in patients with PD, but unfortunately, no specific treatments for these difficulties have been developed.

Autonomic changes are often seen in patients with PD, including constipation, orthostatic hypotension, urinary urgency, and erectile dysfunction. Constipation can be quite disabling and may precede the onset of motor signs by many years.[131] Symptomatic orthostatic hypotension is related to the duration and severity of the disease and may be exacerbated with higher levodopa doses and dopamine agonist use.[132] Behavioral measures are initial therapy, but many patients may require the use of fludrocortisone (a mineralocorticoid that serves as an intravascular volume expander) or midodrine (an alpha 1–adrenoreceptor agonist).

Patients with PD are at increased risk for hallucinations. Perceptual abnormalities may occur in up to 40% of the PD patients. They consist of a sensation of a presence (person), a sideways passage (commonly of an animal), or illusions. Formed visual hallucinations are present in 20%, and auditory hallucinations are present in 10%.[133] Visual hallucinations are associated with several underlying characteristics of patients with PD including disease severity, dementia, depression, and worse visual acuity.[134] Hallucinations may be related to the underlying disease process or a complication of medications, particularly the dopamine agonists. Treatment of hallucinations and delusions in PD can be reduction of medications, or addition of atypical neuroleptics, specifically clozapine and quetiapine. These two medications are more selective dopamine blockers and therefore have fewer extrapyramidal side effects. Both quetiapine and clozapine have been shown to be effective in the treatment of drug-induced psychosis in PD.[135,136] The extrapyramidal effects of the antipsychotics may result in more "off" time for patients and noctural ambulation abilities need to be considered.

Sleep disorders are common with PD patients and may precede motor signs by many years.[137] These include REM sleep behavior disorder, fragmented sleep, insomnia, circadian rhythm disturbance, excessive daytime sleepiness, and restless legs syndrome. REM sleep behavior disorder may range from harmless muttering to fighting with imaginary people in the room. Patients may fall out of bed or bed partners may be injured. If REM sleep behavior disorder is suspected, agents such as clonazepam may be useful.[138] Insomnia and fragmented sleep may be related to PD medications or nocturia, but it may also be a sign of a psychiatric disease such as depression.[139] Treatment is aimed at the underlying issue.

Dementia is common among patients with PD, with an average prevalence of 40% in cross-sectional studies and a cumulative prevalence approaching 80%.[140,141] The pathological correlates of dementia associated with PD are not fully established, but numerous Lewy bodies are found outside of the substantia nigra, and in most cases, amyloid plaques and neurofibrillary tangles are present.[142,143] Neurochemically, cholinergic deficits are the most consistent findings associated with cognitive and neuropsychiatric symptoms.[144,145] In cases where the cognitive difficulties have been optimized by dopaminergic therapy, the initiation of a specific cognitive therapy may be useful. Rivastigmine was associated with moderate improvements in dementia associated with PD but also with higher rates of nausea, vomiting, and tremor.[146] There may be a modest benefit on aspects of cognitive function on donepezil or rivastigmine.[147] Memantine may slightly improve Parkinsonian symptoms as measured by UPDRS scoring.[148] Further studies of pharmacological interventions for dementia associated with PD as well as other nonmotor signs of the disease need to be done in the future.

Parkinson plus syndromes

The many advances in the understanding of PD have translated into a number of therapeutic options. However, in many of the other Parkinsonian disorders, the understanding and therapies have not yet reached clinical significance. In this section, multiple systems atrophy, progressive supranuclear palsy, cortico-basilar ganglionic degeneration, and dementia with Lewy bodies will be briefly discussed.

Multiple Systems Atrophy

Multiple system atrophy (MSA) is a sporadic, neurodegenerative disorder characterized clinically by various degrees and combinations of cerebellar signs, Parkinsonism, autonomic failure, and pyramidal signs. Clinical evaluation typically reveals a more symmetric Parkinsonian picture than with PD, with prominent and early autonomic dysfunction. Other features that differentiate these patients from those with PD include absence of tremor at initial presentation and lack of a sustained therapeutic response to levodopa.[149] Early dysautonomia is usually the most disabling feature ofthe disease, particularly postural hypotension. Patients with MSA have a median survival of 6 years, significantly lower than patients with PD.[150]

Dopamine deficits produce much of the Parkinsonism, but other pigmented neurons that involve the cholinergic and adrenergic systems are also involved. Centrally, there are decreased levels of the neurotransmitter metabolites homovanillic acid (HVA), 5–hydroxyindoleaceticacid (5–HIAA), and 3–methoxyhydroxyphenylethyleneglycol (MHPG) in MSA.[151] Peripherally, parasympathetic cholinergic failure presents as constipation, dry mouth, a constant pulse rate, urinary retention, and early erectile failure in men. Sympathetic noradrenergic failure presents as orthostatic intolerance and orthostatic hypotension.

The main neuropathological features that define these disorders are the glial cytoplas mic inclusions (GCIs).[152] Glial cytoplasmic inclusions have been described in oligodendrocytes of the basal ganglia, cerebellum, and autonomic nuclei.[153] In addition to dopamine as the primary neurochemical abnormality, MSA shares alpha-synuclein pathology with PD as it is the major component of GCIs.[154]

Thirty to 40% of MSA patients experience a definite response to levodopa, but only 5% of patients still respond after 5–6 years of therapy.[155–157] A small trial with amantadine at 400 mg/day in 8 participants with clinical MSA unresponsive to levodopa did not demonstrate a significant clinical response.[158] Anticholinergic medications or botulinum toxin injection may be useful when sialorrhea is severe and disturbing. Postural hypotension often responds to elimination of antihypertensive agents, increased salt and water intake, sleeping in a head-up (30°) position, use of waist-high elastic stockings, and treatment with fludrocortisone, midodrine, or pyridostigmine.[159–160]

Progressive Supranuclear Palsy

In 1964, Steele, Richardson, and Olszewski described progressive supranuclear palsy (PSP) as a clinicopathological entity.[161] Typically, PSP patients present with early postural instability, voluntary vertical gaze palsy with intact oculcephalic reflex, pseudobulbar affect, and subcortical dementia. Parkinsonism is manifested by bradykinesia and axial more than limb rigidity with little response to levodopa therapy.

Progressive supranuclear palsy patients have dysfunction of dopaminergic, GABAergic, cholinergic, and noradrenergic pathways.[162] Motor disorders are felt to be due to a dysfunction of dopaminergic striatal transmission resulting in inhibition of the direct striatal pathway and activation of the indirect striatal pathway. The presence of more diffuse lesions involving the globus pallidus, putamen, and subthalamus may be responsible for the absence of response to levodopa. In addition, dopamine and HVA concentrations are reduced in the caudate nucleus and putamen as well as reduced numbers of dopamine receptors. Choline-O-Acetyltransferase (ChAT) activity is decreased in parallel fashion in all basal ganglia structures.

Neuropathologically, PSP is characterized by abundant neurofibrillary tangles and/or neuropil threads in particular areas of the basal ganglia and brain stem; neuronal loss and gliosis are variable. Neurofibrillary tangles, neuronal loss, and gliosis in PSP particularly affect the striatum, pallidum, subthalamic nucleus, substantia nigra, oculomotor complex, periaqueductal gray, superior colliculi, basis pontis, dentate nucleus, and prefrontal cortex.[163]

Dopaminergic replacement therapies are usually only transiently or mildly effective in PSP. They should still be tried when patients have Parkinsonism because lack of sustained and/or marked benefit from levodopa therapy effectively rules out PD and may also support the diagnosis of PSP. Amitriptyline and amantadine can improve some PSP symptoms, but anticholinergic effects can damage cognitive function and ambulation, and their use must be limited only to few particular indications (e.g., hypersalivation, pseudobulbar affect).[164] Neither noradrenergic drugs nor cholinergic replacement therapy with donezepil, a centrally acting cholinesterase inhibitor, has improved PSP symptoms.[165] Reduced neurotransmission of GABA in the striatum and globus pallidus may contribute to the symptoms of progressive supranuclear palsy. Drugs that act specifically on the GABAergic system, such as zolpidem, have produced some improvement of motor symptoms in patients with PSP.[166]

Cortical-basal Degeneration

Cortical-basal degeneration (CBD) typically presents as a levodopa-resistant asymmetric akinetic-rigid syndrome associated with apraxia, cortical sensory loss, and alien limb phenomenon. The most common Parkinsonian sign noted is rigidity, followed by bradykinesia, gait disorder, and rarely, tremor. The majority of cases are women and higher cortical dysfunction occurs in most patients.

Neurochemically, the neurotransmitters involved with CBD have not been extensively studied, in part due to the rarity of the disease. Pathologic evaluation typically shows asymmetric frontoparietal atrophy. The disease is characterized histologically by neuronal loss, gliosis, and a distinctive neuronal change consisting of swelling of the cell body

that is resistant to staining methods (achromasia).

Levodopa therapy can improve clinical signs in some patients while dopamine agonists, selegiline, and amantadine may provide less benefit. Other potential supportive therapies that can be used include benzodiazepines for myoclonus and botulinum toxin injections for dystonia.

Lewy Body Disease

Lewy body disease (LBD; also referred to as dementia with Lewy bodies) manifests with memory, attention, executive function, and visuospatial difficulties that are associated with Parkinsonism. By definition, there must be Parkinsonism and dementia that start within one year of each other, but these symptoms can often be difficult to elicit clinically. Other major features of the disease include the presence of REM sleep behavior disorder, severe neuroleptic sensitivity and low dopamine transporter uptake on SPECT imaging.[167] Frequently, hallucinations or other psychotic features are present early in the disease, with or without dopaminergic therapy.

Lewy body disease involves multiple neuronal systems through the formation of intraneuronal inclusions consisting of alpha-synuclein. These collections are the same Lewy bodies seen in PD, but they are more extensive and involve cortex as well as subcortical and brainstem structures. Although LBD exhibits a clinical phenotype apparently different from PD, the morphology of Lewy bodies, the characteristics of the vulnerable neuronal types, and the distribution of affected subcortical nuclei and cortical areas closely overlap with those of PD.168,169

Levodopa can be used for the motor disorder of both LBD and PD. Approximately one third of patients may respond to levodopa therapy, with a larger proportion of the younger patients responding.[170] However, the response to levodopa was less than in patients with PD. Rivastigmine can improve apathy and anxiety as well as reduce delusions and hallucinations.[171] Atypical antipsychotics such as quetiapine and clozapine may be useful in LBD, but controlled clinical trials are needed.

Huntington's disease

Clinical Manifestations

Huntington's disease (HD) is characterized by the insidious onset of the triad of movement disorders, behavioral manifestations, and psychiatric disease. Typically, chorea and dystonia involve the extremities and trunk but can also impact the head, neck, and face. In addition to the hyperkinesias, patients may also have increased tone and bradykinesia. In the Westphal variant of HD, bradykinesia and dystonia can predominate with the presence of a low frequency tremor. Men and women are affected equally and typically in the third and fourth decades. However, the symptoms of HD can start at any age with reports ranging from 2 to 90 years.

Huntington's disease is caused by a CAG (glutamine) trinucleotide expansion in exon 1 of the huntingtin gene at the location 4p16.9.[172] The function of huntingtin is not known, but it may be involved in internal cell signaling and maintenance of CREB binding protein and preventing neuronal toxicity.[173] Penetrance is thought to be 100%, but the American College of Human Genetics has published guidelines on the interpretation of number of repeats.[174] Allele sizes of < 27 are not associated with HD. Patients with an allele repeat size of 27–35 have demonstrated meiotic instability, particularly in sperm, indicating that the following generation is at higher risk of inheriting an abnormal number of repeats. Cases of HD have been reported with as few as 36 repeats. However, 39 repeats and above are typically considered within the HD range. The length of repeat size correlates generally with the age of onset, but not necessarily with the severity or duration of disease[175] (Figure **2–7**).

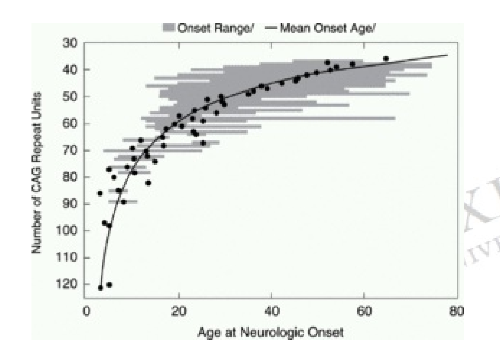




Figure 2–7.
Correlation of number of CAG repeats with age of onset in Huntington's disease. This figure was published in Gusella J. Huntington's disease: CAG genetics expands neurobiology. *Curr Opinion Neurobiol*. 1995;5: 656–662. Copyright Elsevier, 1995.

The course of the disease is typically 15–20 years, with dementia, mutism, dystonia, and bradykinesia predominating in end stages. Cause of death is typically related to complications of immobility such as skin breakdown, pneumonia, cardiac disease, or infection. However, 25% of patients will attempt suicide, and it will be a cause of death in 8%–9% of cases.[176] Huntington's disease is invariably fatal.

The discovery of the gene has led to the possibility of presymptomatic testing. This testing raises serious ethical and social issues and should only be undertaken by experienced clinicians, typically in conjunction with social work, genetics counseling, neurology, and psychology/psychiatry. Delaying or preventing the onset of disease also has become a possibility since clinicians can determine who has inherited an expanded number of repeats, although no trials have yet been conducted in this area.

Control of the behavioral symptoms may be beneficial to not only the patients but also the caregivers. Behavioral techniques can be used and pharmacologic agents can augment the treatment of disruptive behaviors. Depression, anxiety, aggressive, impulsive, and obsessive-compulsive behaviors also need to be treated pharmacologically and behaviorally.

Neurotransmitter and Receptor Changes

There is a sequence and pattern that has emerged in studies of neurodegeneration in HD. Initially, prior to any clinical signs, there may be loss of cannabinoid and adenosine A2a recpetor binding in the striatum and Gpe. There is also increased GABA-A receptor binding in the Gpe. As the disease progresses, there is loss of D1 receptors in the striatum as well as cannabinoid and D1 in the substantia nigra. Finally, in the advanced stages of HD, there is an even further depletion of cannabinoid and D1 receptors in the basal ganglia as well as increased GABA-A receptor binding in the Gpe.[177] There may also be preferential loss of enkephalinergic striatal neurons that correlates with the appearance of choreic movements.[178,179] Loss of substance P/dynorphin neurons in the later stages of the disease correlate temporally with the appearance of dystonia.[180]

GABA

Early neurochemical studies of HD patients/animal models reported significant losses of the amino-acid neurotransmitter GABA in the striatum.[181] Subsequent studies have disputed this finding, but at the time of pathology in HD patients, there appears to be a loss of GABA-producing neurons in the striatum.[182,183] GAB-Aergic neurons expressing dopamine receptors in the striatum predominantly degenerate in HD patients, with layers of cerebral cortex being affected to a much lower extent and striatal

interneurons (mostly nicotinamide adenine dinucleotide phosphate [NAPDH]-positive and ChAT-positive) being spared. Aberrant DA metabolism and transmission might also underlie the clinical manifestations of HD.[184]

Changes in multiple neurotransmitter receptors have been identified in HD striatum including decreases in glutamate, dopamine (D1 and D2), g-aminobutyric acid (GABA-A), adenosine A2A, cannabinoid, and muscarinic cholinergic receptors.[177,185–190]

Glutamate

Huntington's disease brains demonstrate reduced glutamate receptors (GluRs) although this loss may represent generalized neuronal loss.[19,20] Studies have supported a decrease in the R1 and R3 GluRs with relative sparing of the AMPA, NMDA-NR1, and R5 receptors.[190]

Dopamine

In presymptomatic patients with HD, dopamine receptors are decreased, and D1 and D2 receptor mRNA species are decreased in a grade 0 postmortem HD brain.[191–193] Huntington's disease mice with full-length repeats have reduced levels of D2 receptor binding sites in the striatum.[194] Positron emission tomography studies have revealed reduced levels of dopamine D2 receptors in the caudate and putamen of asymptomatic mutation carriers, coincident with reduced glucose metabolism.[191,195]

Neuropeptides, opiates, and other neurotransmitters

Evidence exists that there are early decreases in the neuropeptides enkephalin and substance P, which are used by striatal projection neurons.[196] Substance P tends to be colocalized with GABA in medium spiny neurons while enkephalin is colocalized with another set of GABA neurons that project to the lateral globus pallidus.[179]

Selective Vulnerability

Pathologically, HD results in loss of neurons globally, but cell loss starts in the tail of the caudate. Medium spiny neurons in the striatum that contain GABA and enkephalin are affected early in the disease. These neurons typically project to the lateral globus pallidus. There is then progression to the remainder of the caudate and basal ganglia with subsequent dissemination. There are intranuclear and cytoplasmic inclusions of the aggregate protein huntingtin. Huntingtin is cross-linked with other soluble huntingtin to form the inclusion bodies in neurons. It is not known if the accumulation of huntingtin results in cell death, or if the soluble form of the protein conglomerate is the toxic form. In advanced cases, the cortex, and most basal ganglia structures, including substantia nigra, become involved.

Rationale for Therapy

There are no known therapies that slow the progression of symptoms or change the course of HD. However, there are symptomatic treatments that have been used. There is evidence that antioxidants and mitochondrial-related supplements such as Coenzyme Q10, creatine, or ethyl-eicosapentaenoate (ethyl-EPA) may impact the course of disease.[197,198] Similarly, the impact of agents that may affect adenosine or cannabinoid receptors deserve further study.

Current treatments are aimed at ameliorating specific symptoms. There are multiple agents that have been used to suppress chorea including dopamine receptor antagonists (such as haloperidol), tetrabenazine, clozapine, amantadine, riluzole, and clonazepam.[199–204] Antidepressants and antianxiety agents are commonly necessary but should be used with caution for only the duration of the symptoms. Patients with chorea and psychotic symptoms may benefit from dopamine receptor antagonists. Huntington's disease is a progressive disease that requires frequent reassessment of the prescribed therapies.

For patients with the akinetic form of HD, anti-Parkinsonian medications such as levodopa or dopamine agonists may be beneficial. Botulinum toxin can be used for focal dystonia associated with HD.

Wilson's disease

Clinical Manifestations

Wilson's disease (WD) is an autosomal recessively inherited disorder of copper metabolism. Due to the absence or dysfunction of a copper transportation, copper accumulates in the liver, brain, and eye. Numerous cognitive, psychiatric, and movement disorders may be seen with this disease. The neurological manifestations of WD include tremor, dystonia, ataxia, and dysarthria. Tremor is classically a proximal or "wing beating tremor." Liver function abnormalities in the face of low ceruloplasmin and high urinary copper levels should prompt a diagnosis of WD. Slit lamp examination may reveal Kayser-Fleischer rings and MRI often shows abnormal low T2 signal in the basal ganglia. The typical patient presents in early or middle adulthood with hepatic, psychiatric, and/or neurologic symptoms, but the disease can present in adolescence. The psychiatric or neurologic symptoms may rarely precede the diagnosis of hepatic dysfunction and occur in about 50% of patients.

The diagnosis is made based on the presence of clinical symptoms, potentially family history, and copper studies. Plasma ceruloplasmin levels are low or absent. Serum copper levels may be normal and are not considered useful in diagnosis but can be helpful in monitoring response to treatment. The most useful diagnostic tests in addition to ceruloplasmin are 24–hour urine collection to examine for copper excretion and the slit lamp examination for Kayser-Fleischer rings.

Neurotransmitter and Receptor Changes

There are no clear studies on neurochemical changes in patients with WD. However, the genetic abnormality responsible for the disease was discovered on chromosome 13.[205–207] The gene is highly expressed in the liver, kidney, and placenta and encodes a transmembrane protein ATPase (ATP7B). Defective ATP7B function results in hepatic copper accumulation, which leads to the hepatic and neurological features of WD.[208] In the brain, copper accumulates predominantly in basal ganglia, subthalamic nuclei, and gray and white matter.

Rationale for Therapy

There are four treatment approaches: dietary therapy, therapy to reduce copper absorption, therapy to increase copper chelation, and liver transplantation. Dietary therapy involves avoidance of high copper-containing foods such as shellfish, liver, nuts, chocolate, and mushrooms. Inhibition of intestinal copper absorption using oral zinc supplementation is part of maintenance therapy.[209] At a dose of 150 mg/day in three divided doses, zinc induces intestinal cell metallothionein production, which then forms a mucosal block for copper. Tetrathiomolybdate can also block the absorption of copper by binding copper to albumin in the gut, which is then secreted in the feces. It also is absorbed in the blood stream and acts as a chelating agent through binding of free copper making it unavailable for cellular uptake.

Copper chelation therapy with penicillamine has been available since the early 1950s. Trientine or triethylene tetramine dihydrochloride is a less potent copper chelating agent, but there is a lower likelihood of acute worsening. Both of these treatments have significant risks including the possibility of severe (and potentially irreversible) worsening prior to improvement. There can be significant dermatologic, nephrotic, and immunologic side effects.[210]

Liver transplantation for fulminate hepatic failure in WD occurs most commonly in children and young adults. The transplanted liver is free of genetic defects and continued chelation therapy is not necessary. However, the patient will require lifelong immunosuppresion.

Essential tremor

Clinical Manifestations

Essential tremor (ET) is one of the most common movement disorders. It is characterized by the presence of a postural and kinetic tremor of the hands but can also involve the head, voice, lower extremities, and trunk. A family history is positive in one-half of patients. The tremor is typically symmetric, and rigidity and bradykinesia are minimal or absent. There is no significant response to dopaminergic medications, and the tremor tends to worsen with time, typically over years to decades. The diagnosis is made by the clinical examination, but the diagnosis is often confused with PD. Specific features may help differentiate the two diseases (Table 2–4). Imaging studies with computed tomography (CT) and MRI are unrevealing. Positron emission tomography scanning in ET patients reveals overactivation of the cerebellum. It is hypothesized that ET develops when the cerebello-olivary pathways are disrupted. These pathways are relayed by way of the motor cortex and the thalamus to the spinal cord.[211]

Table 2–4 Distinguishing Parkinson's Tremor from Essential Tremor

	Parkinson's Disease	**Essential Tremor**
Tremor type	Rest	Postural
Frequency	5–7 Hz	7–12 Hz
Symmetry	Asymmetric	Symmetric
Family history	Typically negative	Positive in >50% of patients
Primary treatments	Levodopa, dopamine agonists	Propranolol, primidone
Progression	years	decades
Location of tremors	Extremities > axial	Axial (including voice) = extremities



There are no clear neurochemical abnormalities that have been found in patients with ET. However, surgical ablation or DBS of the ventral intermediate (VIM) nucleus of the thalamus has revealed an abnormal firing rate that corresponds with the frequency of tremor.

Selective Vulnerability

Autopsy studies on patients with ET have found no substantia nigra pathology on routine neuropathologic examination. Cerebral arteriosclerosis with ischemic changes was noted in 4 of 20 cases. Mild cerebellar Purkinje cell loss was noted in two; one of those also had ischemic cerebral stroke, and the other had diabetes mellitus and coronary artery disease.[212]

Rationale for Therapy

Medical therapy for ET typically starts with propranolol or primidone. Propranolol is the only FDA approved medication for ET. It is a nonselective beta-adrenergic receptor antagonist. Propranolol may be started at 10 mg/day, and titrated as tolerated to 300 mg/day. The long-acting formulations particularly work as well and are preferred by patients. Side effects include lightheadedness, fatigue, impotence, and bradycardia.[213] Primidone is an anticonvulsant that is metabolized to phenylethylmalonamide (PEMA) and phenobarbital. It is typically started at 25–50 mg at bedtime. Gradual increases for progression of disease may be needed, but the dose rarely exceeds 250mg/day. The mean decrease in tremor as measured by accelerometer was 50%. Side effects include sedation, nausea, fatigue, ataxia, unsteadiness, and confusion.[214] Primidone and propranolol can be administered together when monotherapy does not achieve the desired effect. Approximately 30% of patients will not respond to either of these two medications.[215]

Many patients note that tremor improves or completely abates with ingestion of alcohol. If so, benzodiazepines (such as alprazolam or clonazepam), can also be considered for therapy. Alprazolam is a short-acting benzodiazepine, which improved tremor clinical rating scales by 25%–37%.[216] These patients in particular should be warned against using alcohol alone as medical therapy. In addition, a family history of alcoholism should be noted, as those family members may have had an alcohol-responsive tremor. Other medical therapies that can be tried after first-line agents include gabapentin, mirtazipine, or topiramate (Table 2–5). Gabapentin is an anticonvulsant with structure similar to GABA. When used in doses of 1,200mg/day there was a 77% improvement in tremor as measured by accelerometry. Side effects include lethargy, decreased libido, dizziness, and shortness of breath.[217] Topiramate is an anticonvulsant that blocks sodium channels and potentiates GABA activity. In a double-blind, placebo-controlled trial, a mean dose of 292 mg/day reduced tremor by 29%, compared to 16% of participants in the placebo arm. The most common treatment-limiting adverse events were paresthesia (5%), nausea (3%), concentration/attention difficulty (3%), and somnolence (3%).[218]

Table 2–5 Management of Essential Tremor (Selected Agents)

Medication	**Dosing Range**	**Main Side Effects**
Propranolol	10–300 mg/d	Fatigue, impotence, bradycardia, depression
Primidone	25–1000 mg/d	Sedation, nausea, ataxia, confusion, vertigo
Clonazepam	0.5–6 mg/d	Sedation, confusion
Gabapentin	300–1200 mg/d	Sedation, decreased libido, dizziness
Topiramate	25–400 mg/d	Weight loss, paresthesias, concentration difficulties
Mirtazipine	7.5–45mg/d	Sedation



If oral medical therapy fails, botulinum toxin may be used to reduce tremor amplitude and reduce its severity. The effect of botulinum toxin on limb tremor is modest and is associated with dose-dependent limb weakness, but it may be helpful for tremor of the head.[219] For refractory tremors, DBS of the VIM nucleus of the thalamus can be

considered. This procedure effectively reduces contralateral limb tremor in medically refractory ET, and can be used safely for at least five years.[220]

Ataxia

Clinical Manifestations

Ataxia describes a lack of coordination while performing voluntary movements. There is typically damage to the cerebellum or its afferent or efferent pathways. Patients may present to the physician complaining of clumsiness, inaccuracy, or instability. Ataxia can affect any or all parts of the body, but when ataxia affects the arms and hands, it may cause an irregular tremor due to overcorrection of inaccurate movements. There may also be dysmetria or past-pointing, terms to describe the inability to gauge distance correctly. The ability to perform repeated movement may also be impaired, termed dysdiadochokinesia. Other signs of cerebellar injury include nystagmus, hypermetric and hypometric saccades, scanning speech, truncal titubation, and difficulties with gait and balance. Ataxia may be episodic or chronic, acute or progressive, focal or generalized, or any combination.

Neurotransmitter and Receptor Changes

The cerebrospinal fluid GABA-A, methionine, and choline levels, adjusted for age, are significantly lower in patients with cerebellar ataxia compared with controls.[221] There may also be autoantibodies that deposit in blood vessels in the cerebellum, pons, and medulla in patients with gluten-induced ataxia.[222]

Selective Vulnerability and Rationale for Therapy

Patients with cerebellar disorders contributing to ataxia may show cerebellar degeneration, lesions in the cerebellum, or agenesis of the cerebellum in congenital disorders. In many instances, however, the etiology is not structural. Imaging with MRI of the brain and spinal cord may help to support the diagnosis.

There are a number of different types of damage to the cerebellum. These range from fixed damage (stroke, trauma, hypoxic injury) to chemical, metabolic, and degenerative. Cerebellar injury related to vitamin deficiency (E, B12, and thiamine) can be reversible and should be identified and treated. Most metabolic diseases and mitochondrial disorders causing ataxia are not reversible. One exception is Coenzyme Q10 deficiency, which has been described in patients with cerebellar ataxia, usually with childhood onset and often associated with seizures and myopathy. The symptoms may respond to Coenzyme Q10 treatment.[223]

Celiac disease is a systemic autoimmune illness triggered by the ingestion of gluten, a protein found in wheat, barley, and rye. From a gastrointestinal view, the disease is characterized by villous atrophy in the small intestine. Serologically, there are elevated levels of tissue transglutaminase, antiendomysial antibodies, and antigliadin antibodies. The clinical presentation can vary from no symptoms, to anemia, to various neurological diseases, including ataxia, seizures, neuropathy, dementia, or depression.[224] Up to 16% of patients with celiac disease have ataxia, and gluten sensitivity is found in up to 40% of patients with ataxia of otherwise unclear etiology.[225] The disease appears to be completely treatable by removing gluten from the diet.

There are a number of hereditary cerebellar ataxias, unfortunately most without adequate treatments (Table 2–6). Vitamin E deficiency, which is an autosomal recessive disorder, is an exception to the rule. There is a mutation on the long arm of chromosome 8 resulting in an abnormal alpha tocopherol transfer protein.[226] Vitamin E deficiency is characterized by childhood onset ofataxia, dysarthria, areflexia, proprioceptive deficits, extensor plantar responses, and skeletal deformities.[227] The treatment for ataxia with vitamin E deficiency is lifelong high-dose oral vitamin E supplementation to bring plasma vitamin E concentrations to normal levels. If vitamin E supplementation is initiated early in the disease process, ataxia and mental deterioration may be reversed; if initiated in presymptomatic individuals (e.g., younger siblings of an index case), findings of ataxia do not develop.[228]

Table 2–6 Molecular Genetics of the More Common Spinocerebellar Ataxias (SCAs)[a]

Disease Name	Gene	Locus	Product	Percent of all ADCA	Distinguishing Features (All Have Gait Ataxia)
SCA1	ATXN1	6p23	Ataxin-1	6	Pyramidal signs, peripheral neuropathy
SCA2	ATXN2	12q24	Ataxin-2	15	Slow saccadic eye movement, peripheral neuropathy, decreased DTRs, dementia
SCA3	ATXN3	14q24.3–q31	Machado-Joseph disease protein 1	21	Pyramidal and extrapyramidal signs; lid retraction, nystagmus, decreased saccade velocity; amyotrophy, fasciculations, sensory loss
SCA6	CACNA1A	19p13	Voltage-dependent P/Q-type calcium channel alpha-1A subunit	15	Sometimes episodic ataxia, very slow progression
SCA7	ATXN7	3p21.1–p12	Ataxin-7	5	Visual loss with retinopathy
SCA8	KLHL1AS	13q21	—	2–5	Brisk DTRs and decreased vibration sense

[a] Based on data from http://www.geneclimcs.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=LbPFrqSMQkeVx&gry=&fcn=y&fw=61KB&filename=/profiles/ataxias/index.html.

The episodic ataxias are inherited in an autosomal dominant fashion. Episodic ataxia type 1 (EA1) is related to a chromosome 12 mutation that also encodes for a potasium channel.[229] Clinically, it manifests with myokymia and episodes of ataxia, which last seconds to minutes and may be startle or exercised induced.[230] Phenytoin or acetazolamide can be effective treatments.[231] Episodic ataxia type 2 is due to a mutation in a voltage-dependent calcium channel located on chromosome19. Clinically, patients present with nystagmus. Attacks last longer than in EA1, lasting minutes to hours and may be induced by a change in posture. Patients may also complain of vertigo. As the disease progresses there is permanent ataxia between episodes.[232] Acetazolamide may help to decrease the frequency or severity of attacks.[233]

Dystonia

Clinical Manifestations

Dystonia is a syndrome of sustained patterned simultaneous muscle contractions of agonist and antagonist muscles. It produces abnormal postures that can be that of an

overextension or overflexion of a hand, inversion of a foot, lateral movements of the head, torsion of the spine, fixed grimace, or forceful closure of the eyes. These abnormal movements are frequently repetitive and may be associated with tremor.[234]

Voluntary movements usually aggravate a dystonic movement. It is present usually continuously throughout the day, but increases typically with stress, emotional states, and fatigue and it is suppressed with relaxation and sleep. A sensory trick may often diminish the abnormal movement (*geste antagoniste*). Even though in severe instances it may result in grotesque postures, it is usually painless with the exception of cervical dystonia.

The abnormal simultaneous activity of both agonist and antagonist muscles can affect a limited group of muscles (focal dystonia), adjacent body parts (segmental dystonia), one side of the body (hemidystonia), or two or more segments (multifocal and generalized dystonia). Dystonias may be primary, secondary, hereditary, or sporadic (Table 2–7).

Table 2–7 Classification of Dystonias

I Primary dystonias
- a. Hereditary
  - 1. Generalized
  - 1. DYT1
  - 2. DYT5 (or Segawa syndrome, also called dopa-responsive dystonia)
  - 3. DYT11 (and 15; myoclonus-dystonia)
  - 4. DYT12 (rapid onset dystonia-parkinsonism)
  - 11. Focal
  - 111. Paroxysmal
  - 1. Kinesiogenic
  - 2. Non-kinesiogenic
- b. Sporadic
  - 1. Focal
  - 1. Cervical dystonia (spasmodic torticollis)
  - 2. cranio or orofacial dystonia (Meige's syndrome)
  - 3. blepharospasm
  - 4. spasmodic dysphonia
  - 5. isolated, task-specific limb dystonia
  - a. musician's dystonia
  - b. writer's cramp
  - c. golfer's yip
  - 11. Generalized

II. Secondary dystonias
- a. Associated with neurodegenerative diseases
  - 1. Huntington's disease
  - 11. Parkinson's disease
  - 111. Wilson's disease
  - iv. Pantothenate Kinase-Associated Neurodegeneration (PKAN)
- b. Enzyme deficiencies, storage diseases, and other metabolic disorders
- c. Environmental causes
  - i. Trauma
  - ii. Infection
  - iii. Perinatal
  - iv. Toxins/drugs
  - 1. Carbon monoxide
  - 2. Manganese
  - 3. Dopamine D2 antagonists
  - 4. Cyanide
- d. Dystonia-plus syndromes
- e. Psychogenic

III. Pseudodystonia
- a. Atlanto-axial dislocation
- b. Soft tissue mass
- c. Congenital torticollis

Most cases of primary generalized dystonia are believed to be hereditary. In these patients, dystonia occurs as a solitary symptom and is not associated with an underlying disorder. There are at least 15 different types of inherited dystonia syndromes, most with a well-defined phenotype.[235] Most cases of early-onset primary generalized dystonia are due to a mutation in the DYT1 gene. The gene codes for torsin A, an ATP-biding protein. Although DYT1 has an autosomal dominant pattern of heritability, there is only 30% penetrance.[236] Focal dystonias are far more common that the generalized forms and are usually sporadic. Curiously, the same GAG deletion in the DYT1 gene may be found in patients with focal dystonias.[236]

Dopa-responsive dystonia (DRD or Segawa's disease) is an autosomal-dominant disorder characterized by childhood onset dystonia, often followed by mild Parkinsonian features and a dramatic and sustained response to relatively low doses of levodopa.[237] Similar to other dystonias involving the lower extremities, initial diagnostic confusion with cerebral palsy is common.[238] Mutations in the gene (GCH1) coding for guanosine triphosphate (GTP)–cyclohydrolase I (GTPCH), have been identified in patients with DRD. It is now known that DYT5 is the same disease.[239]

Myoclonus-dystonia is an autosomal-dominant disorder characterized by myoclonus and dystonia that often improves significantly with alcohol intake. Dystonia is usually of the arms, trunk, or bulbar muscles. There is widespread phenotypic heterogeneity and several loci have been identified in families, but the most common etiology is a loss-of-function mutation in the ε-sarcoglycan (SGCE) gene. Association with this disorder and obsessive compulsive disorder has been described.[240,241]

Acute dystonia is commonly drug induced and primarily involves the neck and eyes. After the administration of a dopamine blocking agent, patients develop an acute onset of a painful dystonia that can last hours and recur. Prolonged exposure may also lead to tardive dystonia, even after discontinuation of the medication.[242]

Neurochemical Pathology

The pathophysiology of dystonia is unclear. Lesions in the lentiform nucleus of the basal ganglia and thalamus (specifically posterior and midline nuclei) are known to cause dystonia, but there is no consistent anatomical lesions in primary dystonia.[243] There may be reduced spinal cord and brainstem inhibition in patients with dystonia. There is also a role for sensory feedback involved in the pathophysiology of the disease (see Figure **2–8**).[244] Functional imaging points to differences in cortical activation of the globus pallidus.[245]

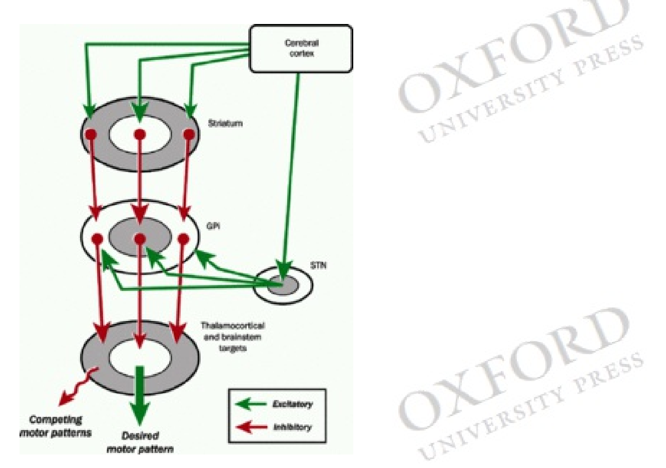




Figure 2–8.
Functional organization of basal ganglia output for selective facilitation and surround inhibition of competing motor patterns. Open arrows indicate excitatory projections; filled arrows, inhibitory projections. Relative magnitude of activity is represented by line thickness. GPi indicates globus pallidus pars interna; STN, subthalamic nucleus. From *Arch Neurol*. 2003;60:1365–1368.[244] Copyright 2003, American Medical Association. All rights reserved.

Dystonia may result as a functional abnormality of the basal ganglia circuitries and their ascending connections to the thalamus and motor cortex and descending to brainstem and spinal cord that leads to slow voluntary movements, excessive and overlapping activity in agonist and antagonist muscles, and overflow of activity to adjacent muscles not normally involved in the movement. Dopamine and receptors are implicated in dystonia, and the D5 receptor is a likely candidate.[246]

Rationale for Therapy

Due to various locations and etiologies of dystonia, the treatment also needs to be tailored to the needs of the patient. There are oral medications that have systemic effect that may be beneficial for a patient with generalized dystonia but intolerable to those with a focal dystonia. Medical treatments for dystonia include the use of anticholinergic agents, benzodiazepines, muscle relaxants (such as baclofen), anticonvulsants, and dopaminergic agents in their whole spectrum: stimulators, blockers, and depleting agents. Generally, all children and young adults with limb onset or segmental dystonia should be given a trial of levodopa, although only a minority of patients will respond.

Acute drug-induced dystonic reactions should be treated by removing the offending agent, usually a dopamine receptor blocker used as an antipsychotic or antiemetic or promotility agent, followed by intravenous administration of diphenhydramine or other anticholinergic agent and benzodiazepines.

A few surgical options can also be considered for severe or medically refractory dystonia: intrathecal delivery via pump of baclofen; selective peripheral denervations such as posterior ramisectomy for cervical dystonia; and two types of intracranial neurosurgical interventions: stereotaxic thalamotomy or pallidotomy and DBS, either thalamic or pallidal. Myotomy and myectomy are treatments that are no longer used for dystonia.

Bilateral DBS of the globus pallidus has been shown to be effective in both children and adults. A prospective double-blind video-controlled study in adults showed sustained improvement in the motor and functional capabilities, decrease in the need of oral medication, and a tolerable profile of side effects. Patients with phasic movements tended to benefit more from DBS than those with tonic posturing.[247]

The primary therapy for most focal and segmental dystonias as well as adjunct therapy for more widespread dystonias is the use of the focal therapy, botulinum toxin (BTX). Botulinum toxin is a neuroparalytic toxin produced by the bacterium *Clostridium botulinum* and inhibits the presynaptic release of acetylcholine at the neuromuscular junction and the parasympathetic end terminals. Therefore, BTX can be used in conditions of overactive smooth muscle and in overactivity of glands. The parasympathetic blockade also has relevance in terms of a potential side-effect profile.[248]

C. botulinuum produces seven serologically distinct toxins that are designated from A to G, but only serotypes A and B are commercially available. In addition to dystonia, BTX has been used for a wide variety of conditions including hemifacial spasm, spasticity, tremor, hyperhydrosis, strabismus, headaches, back pain, achalasia, and many others that involve excessive muscle contraction or autonomic dysfunction.[249]

The recommended maximum body dose per visit varies based on manufacturer and serotype. For Botox® (Allergan), the upper limit is 500 mouse units (MU) while for MyoBloc/ NeuroBloc® (Solstice), a maximum of 25,000 MU are used, based on body part and severity. There is no direct conversion between types of BTX. The degree of weakness depends on the dose, the muscle mass, and on individual susceptibility.

The onset of effect of BTX types A and B is three to five days. The peak effect is generally seen about three weeks after injection. The median duration of clinical effect with BTX type A is three months, although the benefit may last six months or longer if used for hyperhydrosis. The median duration of the clinical effect of type B is also three months but may be of shorter duration when used for cervical dystonia (12.1 versus 14 weeks).[250] There is also electromyograhic evidence in peripheral limb muscle that BTX type B has a shorter duration of action than BTX type A.[251]

After an intramuscular injection, the toxin diffuses along fascial lines in the muscle, with the effect diminishing with increasing distance from the injection site. Smaller neurotoxin complex size and larger dissociated subunits diffuse further, indicating that BTX type B will spread farther than type A.

Botulinum toxin is thought to exert the majority of its action peripherally. However, there is some evidence that BTX can at least transiently alter the excitability of the cortical motor areas by reorganizing the inhibitory and excitatory intracortical circuits.[252]

The injections are generally well tolerated with side effects from the injection itself including a burning sensation and bruising. Where the toxin is injected, there may be excessive weakness causing incomplete eye closure, ptosis, drooping of the head, dysphagia, or other problems from excess local weakness. Distant effects have been demonstrated by EMG, but clinical weakness of distant muscles or generalized weakness is rare.[253,254] Botulinum toxin treatment can also cause dry mouth or dry eyes.

There are no absolute contraindications to the treatment with BTX. It is relatively contraindicated in patients with disorders affecting the neuromuscular junction such as Myasthenia Gravis and the Lambert-Eaton myasthenic syndrome and in patients taking aminoglycosides, as those medications may enhance the blockade of neurotransmitter release. Extreme caution should be taken when applied to patients with motorneuron diseases such as amyotrophic lateral sclerosis and in patients with neuropathies affecting motor fibers, as BTX may increase weakness. It is generally not recommended in patients who are pregnant or breastfeeding, although therapy has not been well studied in this population. In a small case series, it appears to be safe during early pregnancy.[255]

Primary failure after injection of BTX may be due to inadequate dosing, misdiagnosis, injections of inappropriate muscles, contraction of uninjectable muscles, or muscles inhibited by orthopedic-related contractures or suboptimal injection technique. Secondary nonresponders can be classified in two groups: those patients in whom muscle atrophy develops in the injected muscles despite the suboptimal clinical response and those who do not develop atrophy. In the former group, the failure causes are usually the ones described previously for primary nonresponders. In the latter group, the absence of atrophy is equivalent to resistance or failure of the toxin to produce muscle paralysis. Immunogenicity or neutralizing antibody formation is thought to be the causative agent for this type of resistance. Psychosocial factors also need to be considered in any patient with a lack of efficacy, as these may overcome mild to moderate BTX effects.

Antibody formation against BTX type A is described to happen in up to 17% of patients administered Botox® (Allergan) manufactured through 1997. However, since that time, a new formulation has been developed with a rate of antibody formation measured at 0.4%.[256] The lower immunogenicity is likely related to a lower associated protein load.[257] Although less well studied, antibodies to BTX type B can develop in up to one third of patients.[258] Several parameters have been identified as risk factors for the development of neutralizing antibodies: shorter inter-injection intervals (less than every 3 months), more booster injections (injections given within 2–4 weeks) and higher doses at a given injection session.[257,259] There are serological markers for BTX type A antibodies, but a clinical test using the frontalis muscle response to a single high dose typically suffices in the context of adequate dose, location, and clinical resistance.

Botulinum toxin is an excellent therapeutic agent, but to maximize efficacy while minimizing side effects, patients should generally be referred to providers with experience and specific training in administration of BTX.

Conclusion

Movement disorders are a diverse set of diseases that result in either excessive or lack of movement. Many of the anatomical structures involved in the various sporadic and genetic diseases overlap and can be understood somewhat based on structural connections. As our understanding of the underlying pathophysiology increases, more specific treatments and prevention strategies can be developed.

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Epilepsy

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Epilepsy is a common neurological syndrome, surpassed only by Alzheimer's disease and stroke, affecting about one percent of the population in developed countries at any given time, and approximately 2.7 million people in the United States.[1,2] The incidence is highest in childhood, with a modest rise in incidence in adolescence, and a continued increase after age 50, reflecting acquired brain injuries that predispose to seizures. In the elderly population, stroke, dementia, and tumors represent common etiologies. By one estimate, epilepsy may affect as many as 1–2 per thousand by age 80. The economic burden of epilepsy in the United States approaches $17 billion a year in associated health care costs and losses in employment, wages, and productivity,[2] combined with significant social stigma, which perpetuates undereducation and underemployment.[3] In terms of direct impact on health and health-related quality of life, epilepsy is associated with a 2-fold to 3-fold increase in mortality, and causes activity limitations, depression, anxiety, reduction in vitality, and poor rest at rates commensurate with arthritis, chronic heart disease, diabetes, and cancer.[4,5]

Because of the prevalence of epilepsy and its negative impact on the physical as well as psychosocial wellbeing of those who experience recurrent seizures, anticonvulsant drugs are commonly prescribed. Challenges in the use of these medications include identifying drugs that are likely to be efficacious given the presumed type of epilepsy being treated; managing adverse effects; and taking account of drug interactions, not only among anticonvulsants but also among drugs used for concurrent conditions. Although the seizures of most persons with epilepsy can be satisfactorily controlled on a single medication, it is clear that a sizable minority may not be well-controlled. For those whose seizures are not well-controlled on a single drug, subsequent medication trials yield a decreasing likelihood of complete control. Since driving privileges and thus the ability to obtain and maintain competitive employment are in most states dependent on seizure freedom, efficacy is a major determinant of quality of life. However, other factors come into play: psychiatric conditions are more common in persons with epilepsy and are a factor in quality of life, often more so than seizure control if seizures are incompletely controlled.[6] Further, medications used to treat seizures often produce unpleasant adverse effects that may lower quality of life in persons with epilepsy. It is likely true that a minority of persons with epilepsy are both completely controlled and free of adverse treatment effects.

There are several goals of this chapter. We first present a brief classification of seizure types and review the pathophysiology of partial and generalized seizure syndromes. Next, we review the drugs themselves, emphasizing mechanisms of action, indication, pharmacological properties, and interactions, with therapeutic guidelines. Finally, we will consider areas beyond efficacy that constitute special challenges in pharmacotherapy such as treatment of women, including pregnancy; bone health; treatment considerations with elderly patients; treatment of those with coexisting psychiatric disease; the treatment of people with developmental disabilities; and treatment of status epilepticus. Since the previous edition of this monograph, the pharmacological armamentarium for treatment of seizures has more than doubled. This greater variety of choice is offset by the challenge of being familiar with a greater number of medications and their properties.

Classification of seizures, epilepsy, and antiseizure drugs

Epilepsy is a syndrome, a collection of disorders that present similarly, with clinical seizures. Seizures are the result of synchronous discharges in many neurons that occur in discrete episodes—the ictus. Although epileptiform discharges may occur interictally, these are usually brief enough to produce no clinical accompaniment. The manifestation of seizures depends upon the type of epilepsy, whether it is focal in origin or generalized, and, if focal, upon the area(s) of brain involved. In this way, one can classify either seizures—based on the manifestation, such as simple partial seizures with motor symptoms—or epilepsies—such as idiopathic generalized epilepsy of the juvenile myoclonic type (Tables 3–1, 3–2, and 3–6).[7] Partial seizures may be simple (a single symptom or sign, usually with preserved awareness) or complex (usually with impaired awareness or ability to respond). Partial seizures may remain simple, or evolve into more complex seizures: simple to complex, complex to secondarily generalized tonic, or clonic seizures. Those seizures that are classified as primary generalized begin in both hemispheres and include absence, myoclonic, tonic-clonic, tonic, and atonic seizures.



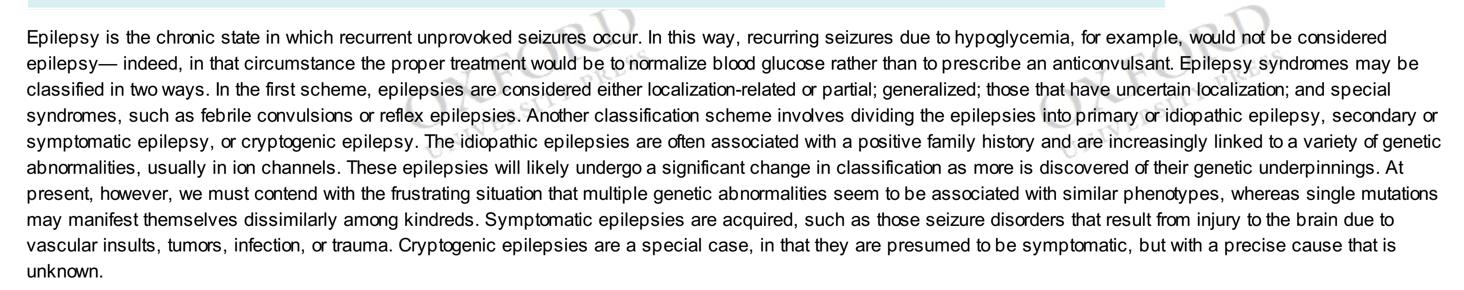
Table 3–1 ILAE Classification of Focal Seizures
• Focal sensory seizures
◦ With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)
◦ With experiential sensory symptoms (e.g., temporo parieto occipital junction seizures)
• Focal motor seizures
◦ With elementary clonic motor signs
◦ With asymmetrical tonic motor seizures (e.g., supplementary motor seizures)
◦ With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)
◦ With hyperkinetic automatisms
◦ With focal negative myoclonus
◦ With inhibitory motor seizures
• Gelastic seizures
• Hemiclonic seizures
• Secondarily generalized seizures

Information from the ILAE commission[7]

Table 3–2 ILAE Classification of Generalized Seizures
• Tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase)
• Clonic seizures
◦ Without tonic features
◦ With tonic features
• Typical absence seizures
• Atypical absence seizures
• Myoclonic absence seizures
• Tonic seizures
• Spasms
• Myoclonic seizures
• Massive bilateral myoclonus
• Eyelid myoclonia
◦ Without absences
◦ With absences
• Myoclonic atonic seizures
• Negative myoclonus
• Atonic seizures
• Reflex seizures in generalized epilepsy syndromes

Information from the ILAE commission[7]

Table 3–6 Seizure/Epilepsy Classification Affecting Choice of Treatment
Partial/Focal-Onset Seizures With or Without Secondary Generalization
Defined by lesion, etiology, or cryptogenic focus
Frontal
Temporal
Occipital
Parietal
Defined by whether awareness is impaired
Simple partial
Complex partial
Partial epilepsy syndromes
Benign childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy) Autosomal dominant nocturnal frontal lobe epilepsy
Generalized-Onset Seizures
Predominant seizure type
Absence
Myoclonic
Tonic-clonic
Tonic/atonic
Idiopathic generalized epilepsy syndromes
Childhood or juvenile absence epilepsy
Juvenile myoclonic epilepsy
Epilepsy with generalized tonic-clonic seizures only
Reflex epilepsies
Generalized epilepsy with febrile seizures plus
Secondary/symptomatic generalized epilepsies
Lennox-Gastaut syndrome
Infantile spasms
Dravet's syndrome
Progressive myoclonus epilepsies
Unspecified symptomatic generalized epilepsy



Epilepsy is the chronic state in which recurrent unprovoked seizures occur. In this way, recurring seizures due to hypoglycemia, for example, would not be considered epilepsy— indeed, in that circumstance the proper treatment would be to normalize blood glucose rather than to prescribe an anticonvulsant. Epilepsy syndromes may be classified in two ways. In the first scheme, epilepsies are considered either localization-related or partial; generalized; those that have uncertain localization; and special syndromes, such as febrile convulsions or reflex epilepsies. Another classification scheme involves dividing the epilepsies into primary or idiopathic epilepsy, secondary or symptomatic epilepsy, or cryptogenic epilepsy. The idiopathic epilepsies are often associated with a positive family history and are increasingly linked to a variety of genetic abnormalities, usually in ion channels. These epilepsies will likely undergo a significant change in classification as more is discovered of their genetic underpinnings. At present, however, we must contend with the frustrating situation that multiple genetic abnormalities seem to be associated with similar phenotypes, whereas single mutations may manifest themselves dissimilarly among kindreds. Symptomatic epilepsies are acquired, such as those seizure disorders that result from injury to the brain due to vascular insults, tumors, infection, or trauma. Cryptogenic epilepsies are a special case, in that they are presumed to be symptomatic, but with a precise cause that is unknown.

Any classification scheme has advantages and disadvantages. What may be helpful in a busy outpatient clinic may not be so helpful for the purposes of research. As our knowledge of seizures and epilepsy grows, classification systems will evolve to accommodate this new information and to aid the clinician and researcher.

The value of classification is proper diagnosis and thus proper treatment. By taking a thorough personal and family history, performing a neurological examination, and using the laboratory— such as electroencephalogram (EEG) and magnetic resonance imaging (MRI)—the diagnosis often can be made. By identifying a seizure type and its associated epilepsy syndrome, treatment alternatives may become evident. For example, if a middle-aged person had a 20-year history of episodic loss of awareness preceded by an epigastric sensation, right temporal discharges on an interictal EEG and MRI evidence of right mesial temporal sclerosis, a diagnosis of localization-related epilepsy and complex partial seizures, with or without secondary generalization could be made. By contrast, if a young person presents with a history of twitching or convulsions, particularly in the morning hours; if there is a positive family history of similar seizures; if the examination and structural imaging are unremarkable; and if the interictal EEG shows generalized frontally predominant polyspike-wave discharges, then juvenile myoclonic epilepsy is the likely diagnosis. If the diagnosis is uncertain despite thorough outpatient investigation, an admission to an epilepsy monitoring unit for video-EEG monitoring may be indicated. By recording the seizure manifestation with its associated EEG, a firmer diagnosis is often possible. In our first case, identifying that the seizure localization is in the right temporal lobe may, if the seizures have been resistant to adequate medication trials, lead to a surgical work-up for a partial temporal lobectomy. In our second case, one would avoid medications that could worsen idiopathic generalized epilepsy, such as tiagabine.[8] Video-EEG monitoring is helpful also in determining whether the etiology of the episodes is epileptic or not; nonepileptic etiologies as different as an insulinoma, cardiac arrhythmia, or psychogenic nonepileptic attacks ought not to be treated with anticonvulsants.

Classification of Antiseizure Drugs

Since the publication of the previous edition of this text, many anticonvulsant drugs have been introduced; this has increased our options for treatment, but has not resulted in any greater clarity in terms of characterizing or classifying the drugs. These drugs are often termed *antiepileptic drugs* or AEDs, but it is more correct to think of them as *antiseizure drugs*, because none of the drugs currently in the U.S. Pharmacopoeia has any demonstrated antiepileptic properties in humans. In other words, these drugs have not been shown to prevent the development or reverse the maintenance of the epileptic state. They are, by contrast, effective at suppressing seizures.

Grouping these medications by chemical structure is similarly unfruitful. While some, like hydantoins (phenytoin, among others) and barbiturates (phenobarbital) have similar chemical structures, this does not readily correlate with clinical indication, efficacy, or side effect profile. Other properties, such as pharmacokinetic properties, or potential for interactions or adverse effects, are useful to know in practice (see further on in this chapter), but have less value as groupings.

In practice, it is helpful to classify antiseizure drugs based on their efficacy for seizure types and epilepsy syndromes (Table 3–3). Thus, relatively few are effective for idiopathic generalized epilepsies (IGEs) and of these, ethosuximide is effective only for childhood absence; others can be used for absence and generalized epilepsies that present with convulsions. Drugs that may be effective for partial seizures with or without secondary generalization may not be the best choice for idiopathic generalized epilepsy either because of relatively poor efficacy or because they have the potential to worsen these syndromes (carbamazepine, tiagabine). Finally, some have a wider spectrum of action, with efficacy for multiple epilepsy types (valproate, lamotrigine, topiramate, levetiracetam, zonisamide).

Table 3–3 Classification of Antiseizure Drugs by Applicable Seizure Type

Drugs for Partial-Onset Seizures	Drugs for Generalized-Onset Seizures
Carbamazepine (Tegretol, Tegretol XR, Carbatrol) Felbamate (Felbatol)	*Broad application and idiopathic generalized epilepsies*
Gabapentin (Neurontin)	Ethosuximide (Zarontin)
Lamotrigine (Lamictal)	Lamotrigine (Lamictal)
Levetiracetam (Keppra)	Levetiracetam (Keppra)
Oxcarbazepine (Trileptal)	Topiramate (Topamax)
Phenobarbital Phenytoin (Dilantin)	Valproate/Divalproex (Depakene, Depacon, Depakote, Depakote ER)
Pregabalin (Lyrica) Primidone (Mysoline)	Zonisamide (Zonegran)
Tiagabine (Gabatril) Topiramate (Topamax)	*Limited to GTC seizures, symptomatic generalized epilepsies or specific syndromes*
Valproate/Divalproex (Depakene, Depacon, Depakote, Depakote ER)	Acetazolamide (Diamox) Carbamazepine (Tegretol, Tegretol XR, Carbatrol)*
Zonisamide (Zonegran)	Felbamate (Felbatol) Oxcarbazepine (Trileptal)* Phenobarbital* Phenytoin (Dilantin)* Primidone (Mysoline)*

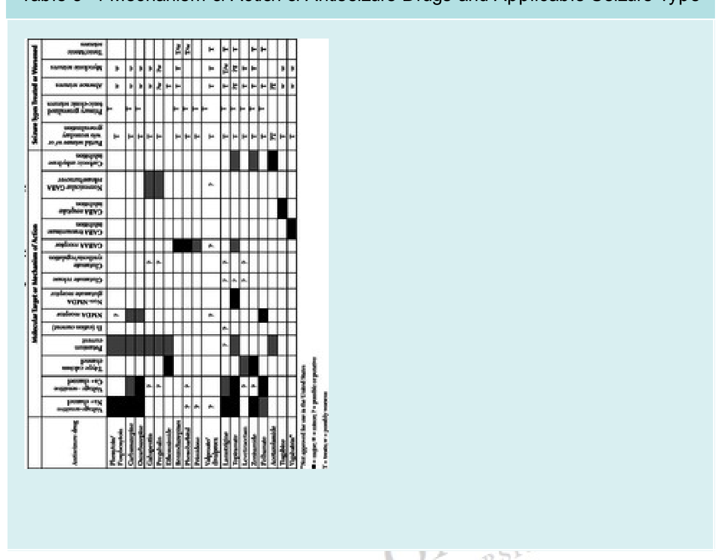
* May worsen some seizure types in generalized-onset epilepsy

The fact that antiseizure drugs may differ in their efficacy for epilepsy syndromes suggests that they may work in distinct ways. While it is true that there are distinct mechanisms of action for these drugs (described further on in this chapter) there is an indistinct correlation between mechanism and clinical indication. Further, while drugs may share a common mechanism, one may be more effective than another in a given patient. This raises the possibility that individual responsiveness to a medication may be multifactorial, dependent on the correct choice of drug for the epilepsy syndrome, individual factors that determine the drug's disposition and elimination from the body, and its mechanism of action, which in turn may be dependent on the type and distribution of its molecular targets in the brain. As the field of pharmacogenetics matures, for example, we may be able to determine whether a person may have a better response to a given medication based on a genetic analysis of the underlying pathogenic process or on the identity of various drug targets.

Mechanisms of Action

Another way to classify antiseizure medications is to consider mechanism of action. This is less useful for clinical decisions than considering the drugs' efficacy for epilepsy syndromes, but can be helpful in choosing multiple drug regimens in a rational fashion by combining drugs with complementary mechanisms of action, as well as for basic understanding of the limitations and characteristics of individual drugs. Generally speaking, antiseizure drugs act in the brain by decreasing neuronal excitation or increasing neuronal inhibition. The major established mechanisms to accomplish these are inhibition of voltage-sensitive sodium channels, enhancement of γ-aminobutyric acid (GABA)-mediated inhibition, reduction of glutamate-mediated excitation, or reduction in the activity of voltage-sensitive calcium channels. Most antiseizure drugs act at multiple targets, several drugs have more novel or putative molecular targets, and some have uncertain mechanisms (Table 3–4). Most of our knowledge of drug mechanism has been derived from basic research using preparations, such as brain slices or neuronal cultures, which may have different properties than neurons in situ. The known mechanisms will be considered in turn, but it is important to recognize that establishing an action of these (or any) drugs in model systems does not necessarily establish that that mechanism is important in controlling seizures, and that establishment of a given mechanism does not necessarily mean that other (yet unknown) mechanisms of action are not relevant. A corollary is that the in vitro conditions by which mechanisms of action are investigated should mimic as closely as possible the conditions that may occur in vivo. For example, the established clinical level of phenytoin in serum is 10–20 μg/ml but because phenytoin is highly protein-bound—about 90%—the relevant in vitro concentration is 1–2 μg/ml. Any action demonstrated at the higher concentration in vitro is less likely to be relevant to its antiseizure effect, although of course it could be relevant to adverse effects occurring at high serum levels.

Table 3–4 Mechanism of Action of Antiseizure Drugs and Applicable Seizure Type



Before reviewing drug mechanisms in more detail, it is useful to consider the pathophysiology underlying seizure disorders, because antiseizure drugs act in ways to counter these dysfunctional changes.

Pathophysiology of focal seizures

There are various causes of focal seizures, all of which result in excessive excitation. Congenital malformations, tumors, infection, traumatic injury, and ischemic insults (among many others) can alter neuronal properties so as to engender the development of epilepsy. The clinical manifestation of this process is an interictal discharge (on the EEG) or clinical seizures, changes in behavior that reflect disruption of the normal function of that part of the brain involved in the epileptic discharge. At a cellular level, seizures occur because of paroxysmal high frequency discharges of action potentials; as local neurons become entrained to fire simultaneously, the seizure focus is established (Figure **3–1**). As the increased excitation caused by the focal discharge is delivered to neuronal networks in proximity to the focus, entrainment of wider neuronal pathways occurs, thus permitting spread of seizure activity and, ultimately, can lead to secondary generalization. This can be seen on ictal EEG recordings, with activity ranging from interictal discharges, without a clinical accompaniment, to regional spread and secondary generalization.

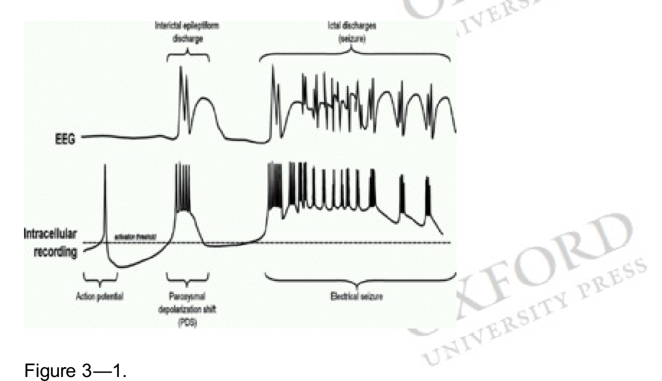


Figure 3—1.
The paroxysmal depolarization shift (PDS) is characterized by excessive and sustained depolarization of groups of neurons and is believed to underlie the generation of interictal EEG discharges. Rhythmic entrainment of networks of neurons into similar activity can result in electrographic and clinical seizures.

The exact mechanisms by which disruption of cellular function results in excessive discharges of neurons are under intensive investigation and our knowledge is far from complete. There may be alterations in the anatomy, physiology, or pharmacology of neurons or glia. For example, in the pilocarpine model of partial epilepsy, changes in the expression of GABA-A receptors occur. Some changes are adaptive, such as increased numbers of receptors (thereby increasing GABA-mediated inhibition). But at least in the hippocampus, the pharmacological properties of those GABA-A channels are different; the channels expressed in the epileptic state are more susceptible to inhibition by ions found in the synapse, such as Zn^{2+}; as GABA-A receptors are inhibitory, a greater reduction in their activity by Zn^{2+} results in a net disinhibition and thus more excitation.[9] Further, these epileptic GABA receptors are less sensitive to molecules such as benzodiazepines (e.g., diazepam or lorazepam), thereby lessening pharmacological inhibition further. Of course, other membrane properties could be affected, such as the properties of other ion channels, whether voltage-sensitive (Na, K, Ca) or neurotransmitter-sensitive (glutamate in addition to GABA). Neurotransmitter receptors that effect cellular processes through linking G proteins could be altered. Glia are sensitive regulators of neuronal activity and recent research suggests that glia may be critical to the development of epileptiform discharges.[10] Finally, there may be many different ways in which epileptic foci develop, depending on the nature of the initial insult to the cortex and that area's network and cellular properties. But the net result is an altered balance between inhibitory and excitatory influences, favoring the latter.

Pathophysiology of idiopathic generalized seizures

By contrast to partial seizures, idiopathic generalized seizures result from rapidly synchronized repetitive electrical discharges across a broad and often centrally integrated neural network. Focal seizures arise from a relatively localized set of hyperexcitable or hypersynchronous neurons, while generalized seizures require the participation of bihemispherically distributed networks of neurons. The classic laboratory manifestation of idiopathic generalized epilepsy is the rhythmic 3 Hertz electroencephalographic paroxysm that occurs synchronously in both hemispheres during absence seizures, briefly arresting behavior and disrupting conscious experience. The exact degree of participation of cortical versus subcortical structures in absence seizures remains the subject of ongoing investigation, but there is widespread agreement that generation of the epileptic phenomenon requires an intact network involving both centrally synchronizing or pacing neurons in the thalamus and hyperexcitable neurons in the cortex. Thalamocortical relay neurons in the thalamus have two basic states of activity dependant on their level of polarization. When depolarized, thalamocortical neurons generate tonic, irregular action potentials in response to excitatory input, transmitting incoming information with fidelity to the cerebral cortex or subcortical structures. When hyperpolarized, thalamocortical neurons enter a bursting mode, firing in rhythmic pulses that are transmitted to cortical neurons in place of accurate transmission of incoming information. Cortical neurons in turn synapse back on thalamocortical neurons providing an excitatory feedback circuit with the potential to generate repetitive discharges. When

thalamocortical relays become overly synchronous a seizure can occur. The electrical state of thalamocortical neurons is regulated by interneurons in the reticular nucleus of the thalamus. Thalamic reticular neurons synapse on GABA-A and GABA-B receptors that hyperpolarize thalamocortical neurons. Hyperpolarization removes inactivation of low-threshold T-type calcium channels residing on thalamocortical neurons that are responsible for their characteristic bursting state. Drugs that block T-type calcium channels are effective in treating absence seizures, and ethosuximide, whose sole mechanism of action is T-type calcium channel blockade, is ineffective against other seizure types.

The mechanisms by which thalamocortical networks are transformed from physiologically functional to dysfunctional epileptogenic circuits vary, but clinical and experimental evidence points to the important contribution of genetically or developmentally altered ion channel function. A majority of IGEs are age-specific, appearing in childhood and with notable exceptions resolving or changing in manifestation in adolescence and adulthood. This likely reflects transient developmental changes in the expression of certain subtypes of ion channels within the system or changes in the organization of synaptic connections.

By definition, IGEs impose little or no neurological dysfunction on patients between seizures. Cognition, neurological examination, and brain imaging are usually normal.

Pathophysiology of symptomatic/secondary generalized seizures

In distinction from IGEs, the seizures of symptomatic or secondary generalized epilepsy arise from a brain that is either structurally abnormal or suspected to be so due to concomitant intellectual or developmental delay. The Lennox-Gastaut syndrome (LGS), one of the more common secondary generalized epilepsies, is characterized by multiple seizure types and a distinctive and highly epileptogenic EEG signature. While there is not a unifying underlying cause for LGS, its pathophysiology likely involves widespread or multifocal epileptogenic zones in addition to aberrant central synchronizing mechanisms. Alternately, generation of generalized seizures from multiple focal epileptogenic zones may occur by means of rapid propagation and secondary generalization of epileptic discharges.[11] The seizures that result can be multiple in type, including tonic, atonic, myoclonic, tonic-clonic, atypical absence, and focal seizures. The implication for treatment is that agents with multiple mechanisms of action—so-called broad spectrum antiseizure drugs—are more likely than those with a single predominant target of action to be effective, although refractoriness to multiple agents, alone or in combination, is common in symptomatic/secondary generalized epilepsies.

Antiseizure Drug Mechanism of Action: General Considerations

Antiseizure drugs exert their effects by modulating the series of electrochemical events responsible for generation of action potentials, the basic phenomenon of neurons that when gone awry, leads to dysfunctional, runaway neuronal excitation, development of an epileptic discharge, and potentially propagation of an epileptic seizure.

At rest, neurons are maintained in a relatively hyperpolarized state with a membrane potential of approximately −65 mV by an energy-dependent Na+-K+ pump that concentrates sodium ions in the extracellular space. Rapid changes in permeability to sodium, potassium, and other ions are responsible for the generation and termination of action potentials, a phenomenon that involves a well-balanced and controlled series of events. When neurons are depolarized to approximately −40 to −50 mV, they reach an activation threshold. Voltage-sensitive sodium channels, which were closed in the hyperpolarized environment, open to allow an influx of sodium ions that rapidly depolarize the cell before they become inactivated. This depolarization activates additional sodium channels that in turn further depolarize the membrane. Voltage-sensitive potassium channels, also closed in the hyperpolarized state, open with depolarization, but more slowly than sodium channels, providing a delayed repolarization and hyperpolarizing phase to the action potential.

In neurons prone to epileptic discharges, there is an abnormally massive and sustained depolarization, the paroxysmal depolarization shift (PDS), that results in rapid bursts of action potentials that can recruit and entrain similarly pathologic excitation among local and interconnected neurons (Figure **3–1**). In basic terms, the process of epileptogenesis is the transformation of a neuron or network of neurons from a system that generates well-regulated action potentials to one that produces hyperexcitable or disinhibited discharges of unusual intensity or duration. The process of epileptogenesis is beyond the scope of this chapter, but changes in intrinsic ion channel properties, dysregulation of ionic and neurotransmitter environments by glial cells, and dysfunctional network reorganization may all contribute.

Individual neurons function within elaborate networks that determine their response and output, features that play an important role in the development of epileptogenesis and propensity for epileptic seizures. But the properties of populations of ion channels, their modulators, and the surrounding electrochemical milieu dictate the behavior of individual neurons, and these remain the chief targets of present drug treatment. As stated previously, compounds used in the treatment in epilepsy are better characterized as antiseizure drugs than antiepileptic drugs. Although the available antiseizure drug armamentarium has more than doubled in the past 15 years, their range of mechanisms has not changed appreciably, remaining generally limited to inhibition of voltage-sensitive sodium channels, enhancement of GABA-mediated inhibition, reduction of glutamate-mediated excitation, or reduction of voltage-sensitive calcium channel activity (Figures **3–2** and **3–3**).

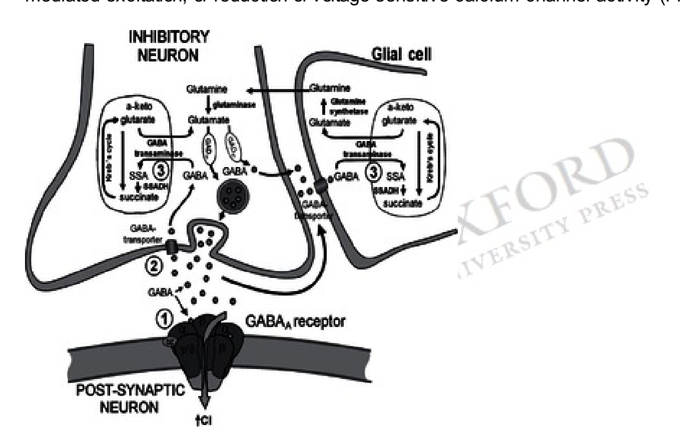




Figure 3–2.
Drug targets for augmenting neuronal inhibition include (1) enhancement of chloride conductance at GABA-A receptors (benzodiazepines, barbiturates, propofol, neurosteroids), (2) inhibition of transporter-mediated GABA reuptake (tiagabine), and (3) inhibition of GABA transaminase-mediated conversion of GABA to glutamate (vigabatrin).

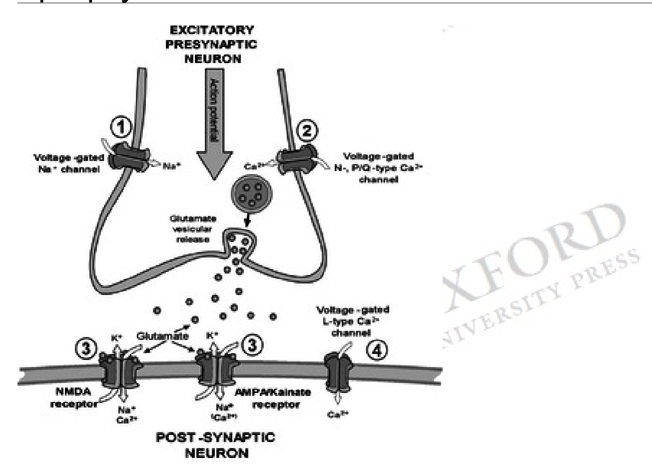




Figure 3–3.
Drug targets for dampening neuronal excitation include modulation of excitatory voltage-gated ion channels and inhibition of glutamate-mediated neurotransmission. (1) Voltage-gated sodium channel blockade prevents fast repetitive firing. (2) Presynaptic calcium channel blockers inhibit vesicular release of excitatory neurotransmitters. (3) Glutamate receptor antagonism directly inhibits excitatory neurotransmission. (4) Inhibition of L-type calcium channels may have mixed effects.

Modulation of voltage-sensitive sodium channel activity

In an epileptic discharge, there is rapid, massive depolarization (the paroxysmal depolarization shift) accompanied by sustained repetitive firing of the neuron. Voltage-sensitive sodium channels play a key role in mediating this phenomenon, and their characteristic activity and kinetics present apt targets for treatment. When a neuron is hyperpolarized in its resting state, membrane voltage-sensitive sodium channels are closed. As the cell membrane is depolarized, as in response to excitation, sodium channels open transiently, allowing rapid inward flow of sodium ions and further depolarization before becoming inactivated. This inactivated state is reversed by repolarization of the neuron.[12] Phenytoin, carbamazepine, and lamotrigine are antiseizure drugs that preferentially bind to the inner pore of sodium channels in their inactivated state, causing them to remain inactive at lower membrane potentials and delaying transition back to the resting, closed state where they are available for reactivation.[13] Antiseizure drugs that preferentially bind to the sodium channel in its depolarized and inactivated state thus have a use-dependent effect, inhibiting neuronal firing most when it is most repetitive and sustained, as is the case with a discharging epileptic focus. In addition to modulating the initial peak sodium current of neurons, antiseizure drugs that bind to sodium channels dampen the persistent depolarization mediated by late opening channels that contribute to the burst firing behavior of neurons undergoing a paroxysmal depolarization shift.[14]

In addition to phenytoin, carbamazepine, and lamotrigine, antiseizure drugs such as oxcarbazepine, topiramate, and zonisamide also act on sodium channels in the central nervous system (CNS).[15–17] At doses and concentrations higher than usually tolerable in an outpatient setting, phenobarbital and benzodiazepines can inhibit sodium channel-dependent firing.Valproate can inhibit sustained repetitive neuronal firing, but by action at a site different than that of phenytoin.[18]

The efficacy and tolerability of one sodium-channel agent as compared to another in any individual patient is difficult to predict. Sodium channel binding agents are not all the same, with different binding potency and kinetics, variability in their interaction with adjacent amino acids, and possibly dissimilar susceptibility to development of drug resistance. Patient-specific factors such as the tolerability of a drug’s side effects can limit attaining clinically significant concentrations of one sodium-channel binding agent while another may produce less adverse side effects. Moderation of voltage-sensitive sodium-channel activity represents an important category of antiseizure drug action, one particularly applicable for treatment of seizures that have a focal onset. But the antiseizure drugs that act on sodium channels are not synonymous with each other and many have additional mechanisms of action and individual characteristics that may enhance or constrain their usefulness in specific applications.

Calcium-channel inhibition

A number of antiseizure drugs act on calcium channels, although in contrast to the clear effect of sodium-channel binding on suppressing the generation and sustention of epileptic discharges, antiseizure drug effects at calcium channels are more variable and in some cases not well-characterized. Like sodium channels, voltage-gated calcium channels are involved in adjustment of membrane polarization, but also have important roles in regulating synaptic activity and neurotransmitter release. There are four major classes of calcium channels in the brain: L-, P/Q-, and N-type channels requiring significant membrane depolarization for activation; and T-type channels that are activated at relatively hyperpolarized membrane potentials.

The function of N- and P/Q-type calcium channels is relatively easy to reconcile with the effects of antiseizure drugs that antagonize their function. Expressed presynaptically, N- and P/Q-type calcium channels control the traffic of calcium that regulates neurotransmitter release. Brief bursts of calcium influx via N- and P/Q-type calcium channels trigger exocytosis of neurotransmitters. When these calcium channels are inhibited, neurotransmitter release is inhibited. The net effect on the neuronal hyperexcitation underlying seizures, however, depends on the context and nature of the synapses involved, since not all neurotransmitter release is excitatory. Lamotrigine, levetiracetam, oxcarbazepine, and topiramate inhibit N-type calcium channels at clinically relevant doses, although the degree to which this mechanism contributes to their anticonvulsant effect is unclear and in the case of levetiracetam likely negligible.[19–22] Gabapentin has putative effects on P/Q-type calcium-channel activity.[23]

Postsynaptic L-type channels concentrated on the soma of neurons allow sustained Ca^{2}+ entry in response to the depolarization of an action potential and are slowly inactivated. The complexity of their function makes predicting the effects of drugs that act on L-type Ca^{2}+ channels difficult. In hippocampal neurons, and in addition to mediating somal depolarization, Ca^{2}+ entry via L-type channels may play an important role in gene regulation and development of long-term synaptic potentiation and epileptogenesis.[24–26] On the other hand, L-type channel-mediated Ca^{2}+ influx helps to trigger the afterhyperpolarization that can reduce excitability.[27] Thus, antagonism of L-type channels with drugs such as carbamazepine, phenytoin, topiramate, and phenobarbital (at high doses) might be reckoned to have either anticonvulsant effects, proconvulsant effects, or both. The actual clinical relevance in terms of seizure control of drugs that bind to and thereby affect Ca^{2}+ channels of different subtypes in specific neuronal locations is unclear.

Transient T-type calcium channels likely play an important, although not altogether unambiguous, role in generating and pacing the hypersynchronous discharges that underlie absence seizures, and are distinguished by their unique property of activation in relatively hyperpolarized states and inactivation by depolarization. As described previously, hyperpolarization of thalamocortical cells results in a transient calcium burst mediated by T-type calcium channels (Figure **3–4**). Drugs that block T-type calcium channels in a use-dependent fashion are useful for treatment of absence seizures, and in the case of ethosuximide, exclusively so.[28] Zonisamide and to some degree lamotrigine have been shown to block cortical T-type calcium channels and also have efficacy against absence seizures.[29] Valproate reduces low-threshold (T-type) calcium currents in extrathalamic neurons, but the role of this mechanism in valproate’s efficacy against absences is uncertain.[30]

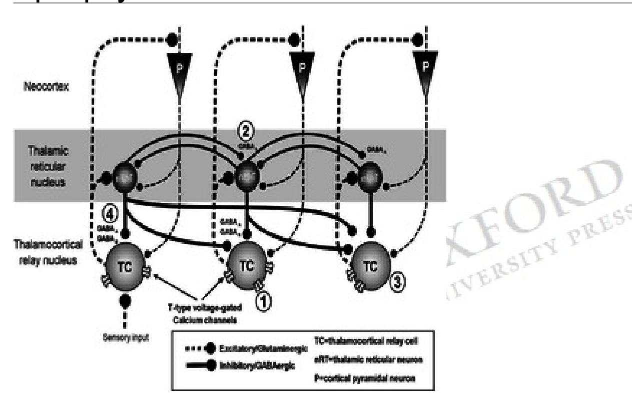




Figure 3–4.
Drug targets for reducing abnormally hypersynchronous thalamocortical networks (absence epilepsy model) include (1) blockade of T-type calcium channels (ethosuximide, zonisamide), (2) activation of some GABA receptor subtypes (benzodiazepines) to desynchronize the network, and (3) modulation of hyperpolarization-induced cation currents (lamotrigine). (4) Drugs that increase total extracellular GABA concentrations (tiagabine, vigabatrin) promote generation of spike-wave seizures via this network.

Potassium-channel regulation

The role of potassium channels in promoting or inhibiting epileptic phenomena and epileptogenesis is complex, as is their variety. As a family, potassium channels regulate the resting potential of neurons, as well as the rate at which neuronal membranes repolarize following an action potential, and thus can modulate neuronal excitability. Major functional classes of voltage-gated potassium channels in the CNS include voltage-gated channels that activate and inactivate rapidly, delayed-rectifier channels that open during depolarization with long latencies before inactivation, and inward-rectifying channels that are closed on depolarization but open at resting potentials. In addition to voltage-gating, some potassium channels are opened by G-protein linked GABA-B receptors that also produce rises in intracellular adenosine triphosphate (ATP) or intracellular calcium. The importance of potassium-channel function in epilepsy has been highlighted by the discovery of inherited disorders such as benign familial neonatal convulsions (BNFC) where mutations in genes encoding potassium-channel subunits result in age-limited idiopathic generalized seizures.

In general, enhancement of outward potassium currents dampens neuronal excitability. Several antiseizure drugs, including topiramate, acetazolamide, and gabapentin, may potentiate potassium-mediated hyperpolarization, although the degree to which these actions contribute to their anticonvulsant effects is uncertain.[31,32] Phenytoin can block delayed rectifier potassium channels, an action that may actually be proconvulsant.[33] Retigabine, a novel anticonvulsant in development, activates KCNQ2 and KCNQ2/3 potassium channels as its proposed primary mechanism of action.[34]

Hyperpolarization-induced cation currents

The hyperpolarization-induced cation current (H-current, *Ih)* is a depolarizing but non-activating cation current activated by hyperpolarization. It is believed to perform oscillatory or pacemaker functions by allowing a graded depolarization following hyperpolarizing events such as inhibitory postsynaptic potentials. A major regulator of neuronal excitability, the strength of I_h is itself regulated by calcium-dependent cyclic adenosine monophosphate (cAMP) levels and can undergo short-term and long-term enhancement or dampening.[35] Permanent changes in I_h caused by prolonged seizures or genetic abnormalities in the nonspecific cation channel proteins (HCN 1, 2, 3, and 4) that mediate it may promote long-term epileptogenic potential. These currents and channels present a potential target for future drug development that has yet to be fully explored. Although not by rational design, lamotrigine has been shown to increase the I_h of pyramidal neuron dendrites, reducing their action potential firing with little effect on firing at the soma.[36] Lamotrigine's effect on the I_h, which participates as a pacemaker mechanism in oscillatory hippocampal and thalamocortical circuits, may in part explain its efficacy against absence seizures, and its broader spectrum of action than other sodium channel blockers such as phenytoin or carbamazepine.

Enhancement of gaba-mediated inhibition

GABA is the predominant inhibitory CNS neurotransmitter, acting at ionotropic GABA-A receptors and metabotropic GABA-B receptors. GABA-A receptors are chloride channels constructed of five membrane spanning subunits, the composition and combination of which determine a given receptor's isoform and its specific kinetics and response to drugs. When extracellular concentrations of chloride are high, activated GABA-A receptors allow a hyperpolarizing influx of chloride cations that inhibit neuronal firing. A membrane potassium-chloride cotransporter (KCC2) maintains the chloride gradient, and when absent, as is the case with immature prenatal neurons, the net effect of GABA-A activation is neuronal depolarization. Similarly, when chloride ions accumulate intracellularly, the inhibitory effect of GABA-A receptor activation is negated or even reversed.

Benzodiazepines act at the GABA-A receptor through specific binding sites presented by α1, α2, α3, or α5 subunits in combination with a gamma subunit. Alpha subunit composition determines the receptor's benzodiazepine affinity, and varies topographically within the CNS, a factor that might determine the differential action of certain GABAergic drugs. For instance zolpidem, a nonbenzodiazepine GABA-A agonist with a high affinity for GABA-A receptors containing the α1 subunit, has strongly sedative but not anticonvulsant effects. Changes in GABA-A receptor subunit composition in some cases may underlie the process of epileptogenesis, and receptor trafficking and degradation is known to play a role in development of drug resistance in status epilepticus.[37,38]

Benzodiazepines increase the affinity of GABA-A receptors for GABA, increasing the frequency of channel opening.[39] This has a use-dependent effect in the setting of epileptic seizures that generate feedback and surround inhibition resulting in high concentrations of extracellular GABA. Barbiturates modulate GABA-A receptor activity by increasing the duration of channel openings, and at anesthetic doses act as direct GABA-A receptor agonists.[40] Similarly, propofol and other anesthetic agents exert their effect by direct activation of GABA-A receptors.[41] Topiramate, in addition to other mechanisms of action, facilitates GABA-A receptor chloride flux.[42] Felbamate enhances the chloride conductance of some GABA-A receptor isoforms.[43]

In certain circumstances dependent on the location and participation of GABAergic neurons in larger networks, enhancement of GABA mediated inhibition can have the net effect of activating rhythmic and hypersynchronous discharges. Such is the case in the thalamocortical reflex loop believed to be involved in generation of absence seizures. Hyperpolarization of thalamocortical neurons occurs in part via postsynaptic inhibitory activation of GABA-A and GABA-B receptors. In this hyperpolarized state, thalamocortical T-type calcium channels produce the calcium bursts that recurrently oscillate by activation of the corticothalamic cells to which they project.[44] When overly synchronous, these oscillations produce absence seizures. Within this circuit, benzodiazepines such as clonazepam preferentially inhibit thalamic reticular neurons and have the effect of desynchronizing the network with a net antiseizure effect, while less specific and indirect GABA-A and GABA-B activation by tiagabine can promote the T-type calcium channel spikes characteristic of this model and act to provoke absence seizures. Indeed, selective activation of GABA-B receptors promotes spike-wave discharges in some models of absence epilepsy.[45]

GABA-A receptors with δ instead of γ subunits may be responsible for low-level tonic GABAergic inhibition, and are insensitive to benzodiazepines, but highly sensitive to neurosteroids, alcohol, and general anesthetics such as propofol. Ganaloxone, a compound in development as a potential antiseizure drug, is an analog to the endogenous

progesterone metabolite allopregnanolone, and modulates GABA-A receptor function through a unique nonbenzodiazepine, steroid-sensitive binding site.[46]

In addition to direct action on GABA receptors, some antiseizure drugs alter GABA trafficking and metabolism. Vigabatrin is an irreversible inhibitor of GABA transaminase, the enzyme responsible for GABA breakdown, and results in increased intracellular GABA stores that can potentiate inhibitory neurotransmission.[47] Its use is limited and restricted by a strong association with irreversible visual field constriction, but compassionate use for devastating childhood epilepsies such as West syndrome continues. Tiagabine increases the concentration of extracellular GABA by inhibiting GABA reuptake, and is not associated with the visual field deficits encountered with vigabatrin, but can be proconvulsant in the setting absence epilepsy for reasons described previously. A preclinical compound, stripentol, inhibits synaptosome GABA uptake, has a barbiturate-like effect at GABA-A receptors, and is used on a compassionate basis in some countries due to its particular efficacy in Dravet syndrome, another catastrophic childhood epilepsy syndrome. Retigabine, currently in development, stimulates de novo synthesis of GABA in hippocampal slices in addition to activation of GABA-A receptors with β2 or β3 subunits.[34]

Glutamate and excitatory neurotransmitter receptors

Glutamate is the major excitatory neurotransmitter in the CNS. Aberrant regulation of glutamate trafficking and expression of glutamate sensitive receptors may play an important role in epileptogenesis, and thus drugs that modify glutamate uptake and regulation may have an antiepileptic effect.[48,49] Vigabatrin, the GABA transaminase inhibitor, can indirectly decrease glutamate synthesis, since the enzyme both catalyzes GABA and forms glutamate from alphake-toglutarate.[50] A potential target for antiseizure drugs that has yet to be addressed is modification of glutamate uptake.

Glutamate acts at three distinct receptor-types: N-methyl-D-aspartate (NMDA) receptors, non-NMDA (alpha-amino-3-hydroxy-5-methy-lisoxazole (AMPA) and kainic acid (KA) sensitive receptors), and metabotropic-glutamate receptors

NMDA receptors are calcium and sodium channels with high affinity binding sites for glutamate and glycine as well as binding sites for zinc and polyamines. They are activated at relatively low concentrations of glutamate, and even by the extrasynaptic spillover of neurotransmitters produced by the excessive synaptic activity of a seizure, and can lead to prolonged depolarization with slow decay to inactivation resulting in burst firing. However, at negative potentials, glutamate binding to NMDA receptors is not sufficient to produce ionic flow due to pore blocking by magnesium. With depolarization the magnesium block is removed. Synaptic activation of shorter latency non-NMDA receptors may produce enough depolarization to remove the NMDA receptor magnesium block, but by then the neuron has often repolarized sufficiently to sustain the block. Thus, NMDA receptors act as coincidence detectors, and when activated by sufficiently sustained excitatory input produce pronged calcium influx on the order of hundreds of milliseconds.[51] Calcium influx mediated by NMDA receptors can mediate protein phosphorylation, resulting in long-term synaptic potentiation, changes in other receptors, and excitotoxic cell injury. Given these properties, NMDA receptors present a conceptually ideal target for antiseizure treatment and in contrast to other targets, antiepileptic or anti-epileptogenic effects. A number of compounds targeting NMDA receptors have proven anticonvulsant in animal models, but development of NMDA antagonists for human use is constrained by their cognitive, motor, and behavioral side effects, highlighting the important role normally functioning NMDA receptors play in learning and motor control. Memantine is low affinity, noncompetitive, NMDA receptor pore blocker used for treatment of dementia, but has no demonstrated efficacy against seizures. Ketamine, another NMDA receptor pore blocker, is a dissociative anesthetic agent that except for rare use as a third-line agent in the setting of refractory status epilepticus, has no practical role as an anticonvulsant.[52] A potential antiseizure drug in development, huperzine A, in addition to reversible anticholinesterase inhibition, acts as a noncompetitive NMDA antagonist at one of the polyamine binding sites of the NMDA receptor.[53]

Although no direct antagonist of the NMDA receptor has yet proven useful for routine clinical use, several antiseizure drugs modulate the receptor's function. In cerebral cortex slices, carbamazepine can block NMDA-induced depolarization,[54] as well as inhibit NMDA-mediated calcium influx in cerebellar granule cells, a property that may contribute to carbamazepine's toxic side-effect profile.[55] NMDA receptors have binding sites for glycine, zinc, and polyamines that affect rates of desensitization, glutamate affinity, and opening kinetics. Felbamate interferes with glycine binding, an obligatory co-agonist for glutamate at the NMDA receptor and thus can reduce NMDA receptor-mediated ion conductance.[56,57] Felbamate's particular efficacy against LGS in children may be due to preferential binding to NMDA receptors containing NR2B subunits, a receptor subtype more abundant in the immature brain.[58] Additionally, relative restriction of NR2B subunit expression to the forebrain in adults may explain felbamate's more favorable neurobehavioral side-effect profile when compared to other compounds acting at the NMDA receptor. Felbamate's use is limited by its unpredictable association with development of potentially life threatening aplastic anemia and hepatotoxicity. An analog of felbamate undergoing development, fluorofelbamate acts by decreasing AMPA and NMDA receptor responses, but potentially without the serious adverse effects of the former.[59]

Non-NMDA receptors are principally associated with sodium channels that mediate fast excitatory neurotransmission. Those comprised of GluR1-4 subunits are AMPA receptors, and those comprised of GluR5-7 and KA1-2 subunits are kainate receptors. Non-NMDA receptors are responsible for a majority of the excitatory glutaminergic neurotransmission in the CNS, and so would seem an ideal target for antiseizure drug development. Kainate receptors, in addition to mediating postsynaptic excitation, are also present on presynaptic axon terminals where they modify glutamate release, and through as-of-yet incompletely elucidated mechanisms, may suppress GABA release from inhibitory interneurons.[60,61] Topiramate, in addition to other mechanisms of action, reduces the excitatory sodium currents of non-NMDA receptors sensitive to kainate, and exerts an early- and late-phase blockade of selective AMPA/kainate-receptor mediated membrane currents, but has no activity at the NMDA receptor subtype.[62,63] Additional compounds specifically targeting AMPA receptors are in development.

Metabotropic glutamate receptors (mGluR) are G-protein linked receptors. Group I receptors are postsynaptic, where they enhance postsynaptic calcium entry, promote calcium release from internal stores, and facilitate depolarization by inhibiting potassium currents. Antagonists to group I mGluR1s are being investigated with enthusiasm for their potential anticonvulsant and neuroprotective effects, but no currently available drugs are known to act by this mechanism.[64] The actions of group II and III mGluRs are more ambivalent in terms of their potential contribution to epileptic events. MGluR1 and mGluR2 inhibit presynaptic release of both glutamate and GABA, and through selectivity of some group II receptors for interneuron GABA synapses, mGluR2 agonism may have anticonvulsant effects.

Carbonic anhydrase inhibition

Transient alkalosis induced by hyperventilation has long been known to provoke paroxysmal spike-wave discharges associated with absence epilepsy. The relationship of agents that induce relative acidosis by inhibition of carbonic anhydrase to prevention of seizures has been less clearly elucidated, although experimental evidence buttresses the concept that lowering pH both increases inhibitory GABAergic chloride currents and suppresses NMDA receptor mediated excitatory currents. GABA-A receptors are sensitive to changes in extracellular pH, and in the presence of GABA produce higher chloride currents in an acidic environment.[65] Lowering extracellular pH can also result in proton blockade of NMDA receptors and suppression of hypomagnesemia-induced epileptiform discharges in hippocampal slices.[66]

Carbonic anhydrase inhibition is the principle action of acetazolamide, an agent that has been used as adjunctive treatment of catamenial and absence seizures. Topiramate and zonisamide weakly inhibit carbonic anhydrase, and this molecular target's contribution to their anticonvulsant effect is less well-delineated than its blame for the gustatory and sensory side effects sometimes encountered with these agents.

Presynaptic neurotransmitter release regulation and presynaptic proteins

Neurotransmitter release is mediated by vesicular exocytosis triggered by presynaptic calcium influx. Indirectly, compounds that inhibit sodium channels can influence the presynaptic depolarization required for voltage-sensitive calcium-channel activation and neurotransmitter release. Indeed, synaptic glutamate release can be inhibited by the action of phenytoin, carbamazepine, lamotrigine, and felbamate on sodium channels.[67,68] While some of these drugs also block calcium channels at supratherapeutic concentrations, and thus more directly influence presynaptic vesicle release, lamotrigine may do so at clinically relevant levels.[69] Presynaptic vesicle trafficking is tightly regulated by synaptic vesicular proteins, including SV2A, the binding site for the antiseizure compound levetiracetam. The nature of levetiracetam's influence on coordination of synaptic-vesicle exocytosis is unclear, but there appears to be a correlation between levetiracetam binding affinity and anticonvulsant efficacy.[70,71] Agents in development,

including brivaracetam and seletracetam, also bind to the presynaptic SV2A protein and may have more potent anticonvulsant effects than levetiracetam based on their higher binding affinity at that site.[72]

Clinical relevance of antiseizure drug molecular targets

The compounds available for treatment of seizures vary in the specificity of their mechanism of action. Most have multiple molecular targets, and the full range and relative contribution of individual mechanisms for a given drug remain to be fully elucidated. The chief mechanism of action of an antiseizure drug roughly correlates with the type of seizure(s) for which it is effective, but predicting its efficacy based on its molecular target(s) is an imperfect reckoning. Table 3–4, which outlines some of the major recognized antiseizure drug mechanisms, illustrates this trend, but also highlights the inconsistency of predicted relationships between molecular targets and clinical efficacy. Drugs that principally act at voltage-sensitive sodium channels and dampen fast repetitive firing tend to be effective against focal-onset seizures and focal seizures with secondary generalization. These include phenytoin, carbamazepine, oxcarbazepine, lamotrigine, topiramate, and zonisamide. Drugs acting on GABAergic systems are less predictable. Clonazepam, a benzodiazepine, directly promotes GABA-A receptor chloride currents and is effective against absence seizures as well as focal seizures. Yet phenobarbital, also acting at the GABA-A receptor in addition to other targets, is not helpful for absence seizures. And those that indirectly enhance GABAergic neurotransmission by promoting GABA release, blocking GABA reuptake, or hindering GABA degradation, tend to be effective for focal-onset seizures, have particular efficacy in certain childhood symptomatic generalized seizures (vigabatrin for infantile spasms), but may worsen absence seizures. Drugs that block T-type calcium channels should disrupt the hypersynchronous thalamocortical oscillations that underlie absence seizures, and potentially the idiopathic myoclonic and tonic-clonic seizures. Valproate, whose T-type calcium channel blockade is mixed with other mechanisms of action, is effective against absence seizures as well as myoclonic and generalized tonic-clonic seizures that in the setting of idiopathic generalized epilepsy have an allegedly thalamocortical mechanism. Yet ethosuximide, a relatively specific T-type calcium channel blocker, is exclusively useful for absence seizures, and ineffective against other seizure types. A number of antiseizure drugs are considered broad spectrum agents, clinically useful for a wide range of seizure types. For many of these, the mechanistic rationale for their effectiveness against individual seizure types is either controversial or obscure.

Supposing direct relationships between mechanism and efficacy is a flawed enterprise, but knowledge about the molecular targets of antiseizure drugs is important for using them wisely. Mechanism of action informs our understanding of antiseizure drug side effects. For instance, GABAergic agents fairly predictably cause some degree of sedation, and glutaminergic inhibitors are often associated with neuropsychiatric dysfunction. Appreciation of drug targets can guide arrangement of rational adjunctive treatment regimens, where antiseizure drugs with putatively complementary mechanisms are combined toward the goal of achieving supra-additive (synergistic) pharmacodynamic efficacy while avoiding supra-additive or additive toxicity. Ultimately, recognizing the imperfect connection between mechanism and application illuminates the bluntness of our tools, a reminder that antiseizure drugs target excessive or hypersynchronous neuronal excitation, not necessarily the pathophysiologic mechanism of individual seizures, and rarely the underlying epileptogenic process.

Clinical use of antiseizure drugs

Establishing a Diagnosis of Epilepsy

Effective therapy for seizures requires a confident diagnosis of epilepsy, identification of the characteristic seizure type or epilepsy syndrome being treated, choice of a drug that best fits the seizure or epilepsy type, appreciation of the pharmacokinetics and side effects of antiseizure agents, and consideration of individual patient characteristics

A number of nonepileptic paroxysmal symptoms can mimic epileptic seizures and should be considered while evaluating a potential diagnosis of epilepsy. These include both physiologic and psychogenic nonepileptic events for which treatment with antiseizure drugs is ineffective, and in place of appropriate treatment, even harmful (Table 3–5). No single diagnostic test supplants the value of a careful clinical history for differentiating epileptic and nonepileptic events. Risk factors for epilepsy include perinatal insult, developmental abnormalities, CNS infections, febrile seizures in childhood, and head injury with loss of consciousness. These should be weighed when considering the differential diagnosis. Perhaps most important is to generate an informative, reproducible narrative of the events themselves, combining the patient’s subjective experience of symptoms with objective observations of how the events occur; their semiology. Beginning with a description that avoids the bias of jargon-laden terminology may help distinguish nonepileptic from epileptic events; in this way the premonitory symptoms and provoking circumstances of vasovagal syncope aren’t tainted by their description as atonic drop attacks. Augmenting the clinical history, the single most useful laboratory test is the EEG. A standard scalp EEG with photic stimulation, hyperventilation (when not contraindicated), and sleep can corroborate the diagnosis of epilepsy and at times facilitate identification of an epilepsy syndrome. In the setting of a single unprovoked seizure, nonepileptiform abnormalities on an EEG are associated with a relative risk of 1.3 for development of epilepsy, and epileptiform abnormities confer a relative risk of 2.0.[73] While the sensitivity of a single EEG for detecting epileptiform abnormalities is only 30%–40%, this increases to more than 80% by the third or fourth EEG. However, care must be taken to accurately correlate abnormal EEG findings with the events in question. Especially in children, epileptiform EEG traits may not be symptomatic. For example, discovery of Rolandic discharges during sleep will not establish a diagnosis of epilepsy that explains a child’s inattention and staring spells at school. Similarly, isolated generalized discharges characteristic of an idiopathic generalized epilepsy trait on an EEG do not provide an epileptic explanation for unilateral anomalies in motor function in an adult. When diagnostic doubt persists, or when initial treatment trials are unsuccessful, long-term video-EEG monitoring remains the gold standard for establishing a definitive diagnosis of epilepsy.

Table 3–5 Nonepileptic Paroxysmal Events
Abnormal movements
Shuddering/jitteriness (infants)
Benign sleep myoclonus
Exaggerated startle response
Paroxysmal torticollis/dystonia
Paroxysmal dyskinesias
Spasticity/clonus
Chorea
Tremor
Tics
Loss or alteration of consciousness
Orthostatic hypotensive syncope
Neurocardiogenic syncope
Cardiac arrhythmia
Metabolic disorders (hypoglycemia)
Drug toxicity/poisoning
TIA
Attentional lapses
Disturbances of sensation or perception
Dizziness
Vertigo
Headache
Dystesthesia/Peripheral neuropathy
Migraine with aura
Transient global amnesia
Sleep disturbances
Narcolepsy/cataplexy
Night terrors
Sleep walking
Sleep-related breathing disorders
REM behavior disorder
Restless limbs syndrome
Excessive somnolence
Behavioral disturbances/irregularities
Rage attacks
Stereotypies (children)
Observational misinterpretation of abnormal or fluctuating behavior (developmental disabilities, autism)
Masturbation
Psychiatric/Psychological
Panic attacks
Acute psychotic symptoms
Fugue and dissociative states
Hallucinations
Psychogenic nonepileptic attacks (PNEA)



Factors Influencing the Decision to Treat

The occurrence of a single provoked or unprovoked seizure does not necessarily establish a diagnosis of epilepsy. In its most recent iteration the International League Against Epilepsy (ILAE) definition of epilepsy is “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures.”[74(p. 470)] Stipulating an “enduring predisposition” acknowledges that seizures occurring in the setting of an acute condition don’t necessarily establish a diagnosis of epilepsy, and may not warrant ongoing treatment. A nonexhaustive list of these includes febrile seizures, acute head injury, metabolic derangement, ischemic or hemorrhagic stroke, eclampsia, drug toxicity, and alcohol withdrawal. In the case of febrile seizures and seizures occurring in the setting of acute head injury, there is good evidence that ongoing prophylactic treatment is not warranted[75,76]. Since a single unprovoked seizure may or may not represent an enduring predisposition for seizures, sorting out the relative risk of developing epilepsy becomes an important undertaking prior to initiating treatment. Depending on whether the population studied clearly excluded subjects with more than one seizure at the time of their enrollment, estimates of the risk of recurrence after a single unprovoked seizure in children and adults range from ~30%–50%.[77]. Randomized, placebo-controlled studies of treatment after a first unprovoked seizure have demonstrated a reduction in early two to five year recurrence risk, but not of recurrence after five years, and perhaps more importantly, no significant impact on long-term outcomes[78,79]. Among patients who have experienced a single unprovoked seizure, those at relatively low risk for recurrence of seizures lack any underlying neurologic abnormality and have a normal EEG. Their risk of recurrent seizures within three to five years is 30%–40% regardless of whether treatment is initiated after the first seizure, while high risk patients have a ~50% chance of seizure recurrence with treatment and a 65% chance untreated[80,81]. Based on these data, there is general consensus that for a majority of low-risk patients with a first unprovoked seizure, treatment should be deferred until the occurrence of a second seizure establishes a diagnosis of epilepsy.

Choice of Antiseizure Medication: Efficacy for Indication

Identifying seizure types and epilepsy seizure syndromes

Once a confident diagnosis of epilepsy is established, the next task is to characterize the seizure type and epilepsy syndrome. Nosology of seizures and epilepsy has moved past the identification of recognizable seizure semiology, through categorization of epilepsy syndromes (an ongoing endeavor), and gradually toward the development of a catalog of genetic cellular and molecular substrates. Lacking proven treatments for the underlying causes of epilepsy, the principle therapeutic target remains prevention of

seizures, and clinical treatment of seizures remains guided and informed by the applicability and efficacy of particular drugs for specific seizure types and epilepsy syndromes. The latter is particularly important for informing patients about prognosis and treatment options, but also may help clarify the mechanism driving seizures that appear similar in semiology but differ in underlying pathophysiology. For instance, the generalized tonic-clonic seizure of a patient with a frontal lobe stroke, a localization-related syndrome, will likely respond differently and to different drugs, than the tonic-clonic seizure of a patient with Juvenile Myoclonic Epilepsy. As described previously, the mechanism of action of an antiseizure drug corresponds only approximately to its applicability to specific seizure types. This connection is further strained by the existence of seizure types that may respond differently to treatment depending on the epilepsy syndrome in which they occur. Since seizures are the signs of a condition, recognition of a "seizure disorder" is comparable in value for therapeutic planning to recognition of a "muscle weakness disorder" or "a coughing disorder," the signs of dysfunction themselves arising from a potentially wide array of underlying pathology. Accurate diagnosis of seizure and epilepsy syndromes is fundamental to effective treatment.

There is considerable debate about how best to classify seizures and epilepsy. The complementary but sometimes competing interests of basic scientists, clinical researchers, epidemiologists, physiologists, pharmacologists, general practitioners, neurologists, and epileptologists are difficult to satisfy within the rubric of any single system. What follows is an attempt to provide a practical guide for antiseizure drug selection derived from basic principles of widely used schemes of seizure and epilepsy classification in clinical practice. As such, it represents the pragmatic "gardeners" and not necessarily the meticulous "botanist's" approach.[82] In practical terms, and considering the overlapping mechanisms of most antiseizure drugs, the degree of diagnostic precision required to make a rational initial treatment choice in regard to efficacy roughly matches that with which most drug efficacy trials have been designed with a few exceptions. Information about which drug to choose comes from multiple sources, including FDA indications, randomized-controlled trials (RCTs), uncontrolled open-label trials, retrospective case series, and consensus of expert experience. The most stringent evidence-based guidelines are limited by the categories employed when selecting patients for study, themselves a mixture of seizure types and epilepsy syndromes, and also by the relative dearth of comparative RCTs of antiseizure drugs for initial monotherapy. Yet the lack of high-level evidence-based consensus has not hindered clinicians from using antiseizure drugs effectively. Similarly, FDA approval, while constraining the licensed indications for which a drug may be marketed, does not always reflect the full range of safe and effective antiseizure drug use. This is particularly so where initial monotherapy indications are considered, the regulations governing how monotherapy trials are performed all but precluding approval of a monotherapy indication for newer antiseizure drugs.

Table 3–6 outlines a minimal, clinically relevant classification scheme for use in choosing an antiseizure drug in most circumstances, and consists of a mixture of seizure types and recognizable common epilepsy syndromes. At the very least, there should be an attempt to distinguish between seizures that are generalized at onset and those that are focal or partial at onset. Practically speaking, subtleties of seizure semiology are not always accurately reported, and at times it may be difficult to make a definitive diagnosis of epilepsy type or epilepsy syndrome. In these cases, care should be taken to avoid drugs that might exacerbate seizures of given subtypes if the occurrence of those subtypes can't be confidently ruled out, and there is good basis for using an agent with a broad spectrum of efficacy for multiple seizure types. While the categories outlined in Table 3–6 simplify and intermix existing diagnostic schemes, they provide a reasonable framework to guide initial treatment decisions, and can be subdivided where relevant into recommendations for adults, children, and the elderly.[83]

Drugs for focal-onset seizures

Focal or partial seizures are those whose semiology is consistent with initial activation or dysfunction in part of one cerebral hemisphere, regardless of their progression or propagation elsewhere. The signs and symptoms of focal seizures correspond to the function of the cortical areas seizing. Motor signs (clonic, tonic, atonic, or dystonic) predominate when motor cortex or its activating structures are involved. Psychic, linguistic, mnemenic, autonomic, or visceral sensory symptoms and motor automatisms can occur when seizures begin in limbic structures, as is the case in temporal lobe seizures. Similarly, seizures arising from parietal or occipital regions produce signs and symptoms that correspond to the functional domain of the involved cortex. In all of these conditions, neuronal excitation at the onset of the seizure may or may not propagate and spread to involve other regions of the brain. The most common sites in the brain where focal-onset seizures occur are temporal and frontal. Seizures arising from the parietal or occipital lobes are relatively rare.

The most dramatic culmination of a focal-onset seizure is secondary generalization, evolution, and propagation over a brief span of time into a generalized convulsion or generalized tonic-clonic seizure. Table 3–1 outlines the ILAE classification of focal-onset seizures.[7] Recognizing manifestations that signify the focal origin of a seizure is critical to distinguish generalized convulsions that are focal in origin from those are generalized at onset, the latter often associated with primary generalized epilepsy syndromes that may be incompletely treated or even exacerbated by drugs commonly used for focal-onset seizures. Unsurprisingly, patients and concerned observers often miss signs of focal seizure onset in the midst of the overwhelming experience of a generalized convulsion. The possible occurrence of prior focal seizure symptomatology should be probed in detail, as subtle subjective aura or lapses in awareness may not be considered relevant by patients to the later occurrence of a secondarily generalized event. In addition to seizure semiology, historical clues assist in gauging whether a generalized convulsion was likely focal in origin. Prior head injury, atypical febrile convulsions, CNS infections, epilepsy onset in adulthood, focal brain lesions on neuroimaging, focal neurologic deficits on exam, and focal epileptogenic findings on EEG increase the likelihood that an ostensibly generalized convulsion was in actuality focal in its onset.

Overall, the drugs most efficacious for partial-onset seizures are those whose chief mechanism of action suppresses fast, repetitive neuronal firing. Drugs with primary or clinically significant action at voltage-gated ion channels comprise the bulk of these, including carbamazepine, oxcarbazepine, lamotrigine, phenytoin/fosphenytoin, topiramate, zonisamide, valproate, and felbamate. Other drugs used for partial-onset seizures, including gabapentin, levetiracetam, phenobarbital, primidone, tiagabine, and pregabalin, have a variety of mechanisms of action, but many act in some way to alter excitatory or resting potentials (Table 3–4). Of this rather large assortment of available and effective drugs for treatment of partial-onset seizures, which one or number of these is the best first choice for initiating treatment? With the exception of rarely occurring genetic focal epilepsy syndromes in adults (autosomal dominant nocturnal frontal lobe epilepsy) and idiopathic focal epilepsy syndromes in children, the localization of focal seizures has little impact on the choice of antiseizure drugs. Rather, the best initial choice of a drug is determined by a series of factors that include drug-specific variables such as efficacy, safety, tolerability, pharmacokinetic properties, formulation, and patient-specific variables (Table 3–7).

Table 3–7 Factors that Affect the Choice of an Antiseizure Drug

Drug-Specific	Patient-Specific	Health System-Specific
Efficacy For seizure type For epilepsy syndrome Monotherapy vs. adjunctive Tolerability Dose-related side effects - lethargy, somnolence - cognitive function - mood disturbance - disturbance of neurologic function - body weight - cosmetic effects Idiosyncratic side effects Safety Serious idiosyncratic reactions - skin - hepatic - hematologic Chronic toxicity - effects on neurologic function - effects on bone - reproductive endocrine effects - teratogenicity Pharmacokinetics Bioavailability Absorption Metabolism/elimination route Drug interactions Dosing requirements Frequency Titration	Age Gender Special populations Comedications Comorbidities Personal preference	Drug availability Drug cost Insurance coverage/formularies

Unfortunately, there is no one drug or handful of drugs that stands out as the unequivocal leader in terms of efficacy and effectiveness. The terms used to commend any individual drug reflect the underlying dilemma native to compounds intended to dampen neuronal hyperexcitability. Efficacy refers to a drug's ability to suppress seizures and is largely unrelated to potency, which refers to the amount of drug needed to produce the effect. Effectiveness is usually a measure of how long a person can safely and tolerably remain on a drug, a reminder that seizures happen to people and a very efficacious antiseizure drug that dulls cognition to an intolerable degree will not likely be an effective long term treatment. The available information on efficacy and effectiveness is derived from an array of sources, including government-regulated indications, evidence-based analyses, and recommendations based on consensus or expert experience. Table 3–8 lists and compares these sources in terms of choosing a drug for treatment of partial seizures. Notably, there are mismatches between FDA indication, strength of evidence base, and common practice recommendations for initial monotherapy. FDA licensing for monotherapy versus adjunctive therapy indications is influenced by increasingly stringent drug trial requirements as well as the resources and interest of pharmaceutical producers for pursuing a monotherapy indication. The quality and number of randomized controlled trials performed on a drug directly affect the strength of the evidence base for its efficacy. And perhaps most importantly for clinical practice, factors such as safety, tolerability, consideration of individual patient characteristics, and ease of use have a strong influence on experience-based recommendations (Table 3–8).

Table 3–8 Comparison of Indication, Level of Evidence, and Common Practice Recommendations for Initial Monotherapy for Partial-Onset Seizures

Drugs for Partial-Onset Seizures With or Without Secondary Generalization

Drug	FDA Indication		Level of Evidence of Efficacy/Effectiveness for Monotherapy[83]					Common Practice Recommendations		
	Monotx	Adjunct	A	B	C	D	E	1st line	2nd line	3rd line
Carbamazepine	■		■					■		
Valproate	■			■				■		
Lamotrigine		■			■			■		
Oxcarbazepine	■				■			■		
Topiramate	■				■			■		
Gabapentin		■			■			■		
Zonisamide		■					■	■		
Levetiracetam		■					■	■		
Phenytoin	■		■						■	
Phenobarbital	■				■				■	
Pregabalin		■					■		■	
Primidone	■					■				■
Tiagabine		■					■			■
Felbamate		■					■			■

Level A: ≥1 class I studies or meta-analysis meeting class I criteria sources or ≥2 class II studies: AED established as efficacious or effective as initial monotherapy

Level B: 1 class II study or meta-analysis meeting class II criteria: AED probably efficacious or effective as initial monotherapy

Level C: ≥2 class III double-blind or open-label studies: AED possibly efficacious or effective as initial monotherapy

Level D: 1 class III double-blind or open-label study: AED potentially efficacious or effective as initial monotherapy

Level E: >1 class IV clinical studies, *or* expert committee reports, *or* opinions from experienced clinicians, *or* absence of directly applicable clinical evidence upon which to base a recommendation

Class I study: RCT or meta-analysis with primary outcome variable of efficacy/effectiveness; treatment duration >48 weeks; double-blind study design; superiority demonstrated or sample size sufficient to show noninferiority no worse than a 20% relative difference in effectiveness/efficacy

Class II study: RCT or meta-analysis meeting all class I criteria except: no superiority was demonstrated and study sample size sufficient only to show noninferiority at a 21%–30% relative difference in effectiveness/efficacy

Class III study: RCT or meta-analysis not meeting the criteria for any class I or class II category

Class IV study: Evidence from nonrandomized, prospective, controlled or uncontrolled studies, case series or expert reports

Common practice recommendations are based on literature review and clinical practice and experience, and may not reflect FDA-approved indications

Key comparison studies and meta-analyses have approached the question of relative efficacy and effectiveness, and are worth noting for the principles of drug choice they illuminate. In the Veterans Administration study of 1985 (VA-I), carbamazepine, phenobarbital, phenytoin, and primidone were compared in partial and secondarily generalized tonic-clonic seizures.[84] Overall, carbamazepine and phenytoin were superior to phenobarbital and primidone, and the differences were largely due to the occurrence of adverse events. All four of these antiseizure drugs controlled tonic-clonic seizures, but carbamazepine controlled partial seizures better than the compared agents. A second Veterans Administration (VA) study (VA-II) compared carbamazepine and valproate for treatment of complex partial seizures and secondarily generalized tonic-clonic seizures.[85] Valproate was as effective as carbamazepine in controlling generalized tonic-clonic seizures, but carbamazepine was superior for control of complex partial seizures and better tolerated in the long term. The results of this trial have likely influenced general practice, positioning carbamazepine as a popular initial monotherapy for partial-onset seizures among clinicians, but the importance of this and similar studies is less their evidence of one antiseizure drug as superior to another and more the demonstration that in general, initial monotherapy with any of the aforementioned drugs is associated with complete or excellent seizure control in ~70% of patients. Addition of a second drug for treatment nonresponders resulted in improved seizure control in 40% of patients, but rarely in seizure freedom. Tolerability was shown to be a central component of drug effectiveness, an effective drug being the one a patient can continue to take with the fewest adverse side effects. The importance of tolerability as an essential factor in choosing an antiseizure drug is further illustrated by another VA cooperative study of initial monotherapy comparing gabapentin to lamotrigine and carbamazepine for newly diagnosed partial-onset epilepsy in an elderly population.[86] Seizure control was similar among these three agents, but significantly more of the patients taking carbamazepine terminated the trial due to adverse events than those taking either lamotrigine or gabapentin. In general, older and newer antiseizure drugs share similar efficacy, but drugs with a more favorable side effect profile will likely be more effective as a first choice.

While there is more to consider than efficacy alone when treating patients with epilepsy, important variables such as tolerability, quality of life, and cost-effectiveness are not consistently studied in a structured fashion. An exception to this rule, and hopefully a model for future study design, is found in the paired SANAD (Standard and New Antiepileptic Drugs) trials for partial-onset and generalized-onset seizures, a multicenter trial conducted in the United Kingdom. Standard and New Antiepileptic Drugs arm A enrolled 1,721 patients over the age of five with partial-onset seizures, and compared seizure control, tolerability, quality of life, and health economic outcomes of initial treatment with either carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate.[87] Lamotrigine had the lowest incidence of treatment failure among these drugs, a result attributable to better tolerability, and statistically significant in comparison to all but oxcarbazepine, for which there were too few patients randomized to allow analysis. Gabapentin and topiramate were the poorest performers of the group. Compared to carbamazepine, considered the treatment standard in common clinical practice, lamotrigine was not clinically inferior in measures of efficacy. Quality of life outcomes were higher in patients experiencing seizure remission and lower with treatment failure. In health economic analysis, lamotrigine was superior to carbamazepine in terms of cost per seizure avoided and cost per quality of life years gained. Overall, the SANAD arm A trial identified lamotrigine as an effective and potentially cost-effective alternative for treatment of partial-onset seizures, and possibly superior to the more traditional carbamazepine as a choice for initial monotherapy.

The studies mentioned here are only representative samples of the kind that inform evidence-based guidelines, but have not established a definitive consensus. There are limits to the utility of current published guidelines for directing clinical practice and a relative paucity of well-designed comparisons of initial treatments. In daily practice, picking the best initial monotherapy for an individual patient is an individualized enterprise, guided in general terms by the available data on efficacy and effectiveness, but given the range of choices available, best directed by the merits and drawbacks of particular drugs applied to particular situations. These factors are described in more detail below in discussion of antiseizure drug pharmacokinetics, side effects, safety profiles, and applicability to special situations and populations. In many cases, choice of the best first drug is a matter of avoiding medications that in a given circumstance are likely to lead to adverse events, intolerance, and ultimately treatment failure.

Drugs for generalized-onset seizures

The underlying causes of partial-onset seizures are myriad, but their etiology has relatively little bearing on the choice of an initial treatment. By contrast, generalized-onset seizures are manifestations of a heterogeneous group of disorders wherein seizure type and the epilepsy syndrome within which the seizures occur strongly influence choice of antiseizure drug as well as which drugs to avoid. Generalized-onset seizures include a number of seizure types: absence, myoclonic, tonic, clonic, atonic, and tonic-clonic as

well as mixtures of these. The electrophysiologic feature common to all generalized-onset seizures is bihemispheric simultaneity of onset manifested in generalized spike-wave, polyspike-wave, or polyspike patterns on EEG. Their underlying pathophysiology involves central and diffuse synchronizing networks. The degree to which cortical versus subcortical structures serve as the primary driver of generalized discharges remains a matter of some debate, but this is of less practical importance than recognizing that generalized-onset seizures represent an electrophysiologic process distinct from that involved in partial-onset seizures. In simplistic terms, partial-onset seizures are driven chiefly by focal neuronal hyperexcitability, and generalized-onset seizures by diffuse neuronal hypersynchrony. As such, generalized-onset seizures as a group respond differently and to different medications than partial-onset seizures.

Generalized-onset seizures are further divided into idiopathic and symptomatic or cryptogenic etiologies (Table 3–6). Idiopathic generalized epilepsies are genetically determined, often begin in childhood or early adulthood, have no recognizable structural or anatomic cause, and occur in the context of otherwise normal neurologic function. Symptomatic generalized epilepsies are associated with functional or structural neurologic brain abnormalities and often with developmental delay. Cryptogenic generalized epilepsies are those where concomitant clinical deficits betray an underlying structural or functional brain abnormality not demonstrable with conventional imaging.

Within the group of IGEs, there are recognizable clinical and electrographic patterns that characterize syndromes such as childhood or juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized epilepsy with tonic-clonic seizures only. When IGE is diagnosed in adulthood, the edges of these syndromic entities may be blurry, producing the less clear-cut picture of a nonspecific idiopathic generalized epilepsy syndrome with mixed seizure types.

Typical absence seizures are characterized by brief lapses in consciousness and behavior lasting approximately 10 seconds and associated with generalized, bilaterally synchronous 3 Hertz spike-wave discharges on the EEG. As a rule, there is no prodrome or warning for a typical absence, and within two to three seconds of the seizure's end, its sufferer returns to normal awareness and perception. Most often, absences are characterized by an isolated lapse in awareness without other clinical manifestations, although subtle facial clonic movements, mild atonic or tonic postures, bilateral facial or manual automatisms, and autonomic phenomena can occur. The existence of these subforms is of little clinical relevance to treatment choice in the absence of other seizure types or concomitant neurologic dysfunction. Produced by hypersynchronous thalamocortical circuitry, typical absence seizures usually respond well to drugs that act on GABAergic mechanisms, specific Ca+ channel receptor targets, or in many cases to drugs that have a broad spectrum of action.[88] Ethosuximide, a T-type calcium channel blocker with lesser effects on potassium currents, is a first-line treatment for typical absence seizures in children under the age of 10, and has no role in the treatment of other seizure types. The common occurrence of other seizure types accompanying absences that persist beyond the age of 10 limits ethosuximide's usefulness in older children or adults. Occasionally ethosuximide can be useful in adults with absence seizures only or as an adjunct in the treatment of mixed generalized seizure types when other medications are ineffective. Through less elegantly characterized mechanisms, and indeed a relevant molecular target that remains elusive, valproate is also highly effective against typical absence seizures, and is another first line treatment in children and adults comparable to ethosuximide in efficacy.[89,90] Many consider lamotrigine another reasonable first-line or second-line treatment for typical absence seizures, particularly where valproate is contraindicated (women of child-bearing potential, given its increased risk of major malformations) or its side effects are undesirable. In a trial of open-label titration then double-blind taper to either ongoing lamotrigine or placebo, control of absence seizures was superior in the lamotrigine arm, although a head-to-head comparison found lamotrigine slightly less efficacious than valproate.[91,92] Effective use of levetiracetam, zonisamide, and topiramate for absence seizures has been reported although not yet studied with sufficient rigor in large groups of patients to allow evidence-based recommendations.[93–95]

Distinguishing the behavioral arrest of absence seizures from that of complex partial seizures is critical to making appropriate treatment choices (Table 3–9). Beyond ineffective, many drugs used for partial onset seizures have been reported to worsen absence seizures, including phenytoin, carbamazepine, oxcarbazepine, vigabatrin, and tiagabine.[96–99] Vigabatrin and tiagabine, for reasons that are interesting from a mechanistic standpoint, have been reported to promote nonconvulsive generalized status epilepticus. These drugs have pharmacological actions that increase neuronal synchrony in thalamocortical circuits.[100–102]

Table 3–9 Differentiating Typical Absence from Complex Partial Seizures

Clinical Criteria	**Absence**	**Complex Partial**
Duration	< 30 s	Often > 1 min
Sudden onset and termination	As a rule	Frequent
Daily occurrence	Common	Rare
Postictal symptoms or impairment	Never	Frequent
Simple automatisms	Frequent	Frequent
Complex behavioral automatisms	Exceptional	Frequent
Sensory hallucinations or illusions	Exceptional	Frequent
Bilateral facial myoclonic jerks or eyelid closures	Frequent	Exceptional
Evolving to other partial seizure manifestations	Never	Frequent
Reproduced by hyperventilation	Frequent	Exceptional
Elicited by photic stimulation	Frequent	Exceptional
Ictal EEG	Generalized 3–4 Hz spike-wave	Focal/lateralized rhythmic discharge
Interictal discharges generalized discharges	Frequent isolated	Sporadic focal discharges
Interictal slowing	Exceptional	Frequent
Normal EEG in untreated state	Exceptional	Frequent

Atypical absence seizures rarely appear as an isolated seizure type, but rather as one of multiple types of seizures in the context of symptomatic or cryptogenic generalized epilepsy syndromes. Clinically, the start and end of an atypical absence event is more difficult to delineate than with typical absences, a feature due at least in part to the challenge of identifying discrete behavioral changes in patients who often have intellectual or developmental disabilities. Most atypical absences last several seconds, but may also be quite prolonged, often intermingled with or preceded by tonic or myoclonic seizures. Electroencephalographically, atypical absence seizures generate slow (1.5–

2.5 Hz) generalized spike-wave discharges that are often less symmetrically distributed and less regular in morphology than those of typical absence. Treatment of atypical absence seizures is governed by recommendations for treatment of the epilepsy syndromes in which they most commonly occur—LGS, myoclonicastatic epilepsy, and continuous spike waves in slow sleep.

Myoclonic seizures present a diagnostic dilemma since myoclonus can arise from either epileptic or nonepileptic conditions. As an epileptic phenomenon, fleeting, shock-like synchronous or asynchronous muscle jerks can affect nearly any part of the body, are potentially generated by nearly any region of the central neuroaxis, and are associated with relatively benign, severe encephalopathic or progressively degenerative neurologic conditions.

Juvenile myoclonic epilepsy (JME) is the most common syndrome associated with myoclonic seizures in adolescents and adults and accounts for approximately 10% of all epilepsies.[103,104] An IGE, JME typically begins in adolescence between 12 and 18 years of age, and while named for its characteristic shocklike muscle jerks, is sometimes not recognized or diagnosed until the appearance of the tonic-clonic or clonic-tonic-clonic seizures that often lag behind the onset of myoclonus by a few years. Absence seizures affect 10%–30% of patients with JME, and often begin earlier in adolescence than the myoclonic seizures.[105,106] Accurate diagnosis of JME is crucial to ensure appropriate treatment, since drugs appropriate for generalized tonic-clonic seizures in other clinical scenarios can worsen the absence, myoclonic and even tonic-clonic seizures of JME. Misdiagnosis of generalized epilepsies as partial epilepsies when tonic-clonic seizures are the predominant seizure type is common, and in the case of JME, the diagnosis is initially missed more often than not.[107–109] Currently, there are no high level, evidence-based recommendations for the optimal treatment of JME. General clinical consensus has long favored valproate as the first-line treatment, and monotherapy with valproate controls the myoclonus and tonic-clonic seizures of JME in approximately 80%–85% of cases.[110,111] Levetiracetam was recently approved by the FDA for adjunctive treatment of JME in patients[12] years and older, and a number of studies suggest that levetiracetam is a reasonable second-line monotherapy choice.[112–114] Lamotrigine has shown efficacy in treatment of JME, and is often prescribed as an alternative monotherapy when reproductive or other side effects of valproate limit its utility.[115,116] Yet while the long-term side-effect profile of lamotrigine may be preferable to valproate, some reports suggest it is less effective than valproate for and can even exacerbate the myoclonus of IGE.[117,118] Topiramate and zonisamide have shown promise in JME, but as-of-yet have limited bases of well-documented evidence or clinical experience.[119–122] A long-acting benzodiazepine with potential for sedative effects that limit its usefulness, clonazepam is effective against the myoclonic more so than the tonic-clonic seizures in JME, and is a reasonable option for adjunctive treatment when myoclonus remains refractory but other seizure types are controlled.[123] Care must be taken with any sedating medication in JME, as drowsiness is a provocative clinical state for seizures. Similarly, sleep deprivation, physical fatigue, alcohol consumption, and even photic stimulation (strobe lights, flashing sunlight) are strong aggravating factors, the avoidance of which may be critical for maintaining seizure control even on the best choice of medications.

Myoclonic seizures can also occur as a fragment of symptomatic or cryptogenic generalized epilepsies, where they are frequently intermingled with tonic, atonic, and absence seizures. The principles for treatment of myoclonus in those settings are dictated by treatment of the relevant epilepsy syndrome and avoidance of drugs that can exacerbate myoclonus.

Generalized tonic-clonic seizures (GTC) can occur as the sole seizure type in IGE, but accurate diagnosis is complicated by the occurrence of GTC seizures in a variety of epilepsies, including those with partial-onset seizures that secondarily generalize and symptomatic generalized epilepsies. Generalized tonic-clonic convulsions excite notice, and are often the manifestation of epilepsy that first prompts medical evaluation. Careful attention must be paid to age of onset, previously unreported coexisting seizure types, aura or partial seizure manifestations, subtle focal neurologic abnormalities, EEG findings, neuroimaging, and risk factors for the development of partial-onset seizures in order to avoid misdiagnosis, mismanagement, and misrepresentation of prognosis. Despite these efforts, a definitive diagnosis is often elusive, and this ambiguity is reflected in the frequent failure to consistently distinguish idiopathic from other etiologies in clinical trials of antiseizure drugs for GTC seizures. The preponderance of evidence-based treatment recommendations applies to seizure type and not to specific epilepsy syndromes. As a result, the recommendations are mixed. The ILAE treatment guidelines identify several drugs with Level C evidence of efficacy for generalized-onset tonic-clonic seizures: carbamazepine, lamotrigine, oxcarbazepine, pheno-barbital, phenytoin, topiramate, and valproate (Table 3–10).[83] Due to limitations of the trials reviewed, the ILAE guidelines do not distinguish between idiopathic GTC seizures and GTC seizures of other etiologies. However, they note Class IV evidence based on review of smaller reports that carbamazepine, oxcarbazepine, and phenytoin can worsen GTC seizures as well as other seizure types when GTC seizures are the predominant seizure type. This apparent paradoxical effect likely reflects the use of these agents in a subgroup of patients with IGE.

Table 3–10 Drugs for Generalized-Onset Seizures

DRUGS FOR GENERALIZED-ONSET SEIZURES							
	FDA Indication		**Level of Evidence*: LevelC (No Level A or B)**	**Common Practice Recommendations**			
Seizure type	**Monotherapy**	**Adjunct**		**1st line**	**2nd line**	**3rd line**	**Drugs that may Worsen Seizures**
Absence	ESM, VPA			VPA, ESM, LTG	LEY TPM, ZNS	CZP, FBM	PHT, CBZ, OXC, TGB
Myoclonic		LEV		VPA	LEV, TPM, LTG, ZNS, CZP	FBM, PB	CBZ, PHT, OXC, GBP, PGB, VGB, TGB, LTG
Tonic-clonic**	CBZ, PB, PRM, PHT, TPM	LTG, LEV	CBZ, LTG, OXC, PB, PHT, TPM, VPA	VPA, LTG, TPM, LEV	ZNS, PHT, CBZ, OXC	PB, CZP, PGB, FBM, GBP, TGB	CBZ, OXC, PHT
Epilepsy syndrome							
Childhood-juvenile-onset absence	ESM		ESM, LTG, VPA	ESM (< 10 years old), VPA (≥ 10 years old)	VPA, LTG	LEV, TPM, ZNS	As above for absence
Juvenile myoclonic		VPA, LEV		VPA	LEY LTG, CZP, TPM	AZM, FBM	As above for myoclonus
Epilepsy with GTC seizures only				VPA, LTG	LEY TPM, ZNS	CZP	As above for tonic-clonic
Infantile spasms	VGT***			ACTH, VGT***	CZP, VPA	LTG, TPM, ZNS	
Lennox-Gastaut syndrome		FBM, TPM, LTG		VPA, LTG	CZP, TPM, ZNS	LEV, FBM, CBZ, OXC, PB	DZP, CBZ, PHT, GBP
Progressive myoclonic				VPA, CZP	LEY TPM, ZNS		PHT, GBP, PGB, CBZ, OXC, TGB
Dravet's Syndrome (SMEI)							LTG

* See Table 3–8 for description of evidence levels.

** Use of some drugs (e.g., CBZ, OXC, PB, PHT) may worsen other seizure types when used for idiopathic generalized tonic-clonic seizures.

*** Vigabatrin is not approved for use in the United States.

ACTH = adrenocorticotropin; AZM = acetazolamide; CBZ = carbamazepine; CZP = clonazepam; DZP = diazepam; ESM = ethosuximide; FBM = felbamate; GBP = gabapaentin; LEV = levetiracteam; LTG = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; PGB = pregabalin; PRM = primidone; TPM = topiramate; VGT = vigabatrin; ZNS = zonisamide.

Common practice recommendations are based on literature review, clinical practice, and experience, and may not reflect FDA-approved indications.

Given the possibility of lingering uncertainty about the exact underlying condition from which GTC seizures arise, a cautious approach commends treatment with drugs that have a broad spectrum of action against multiple seizure types and across a range of epilepsy syndromes. Valproate has traditionally filled this role, but is now accompanied by a number of medications with similar broad spectrum efficacy, including lamotrigine, levetiracetam, topiramate, and zonisamide. In the SANAD trial for generalized or unclassifiable epilepsy, subjects were assigned to arm B and randomized to open-label valproate, lamotrigine, or topiramate if clinical evaluation suggested valproate a better option than carbamazepine, the traditional first-line treatment for unclassified GTC seizures.[124] The rationale for this partition recognizes the uncertainty that remains when clearly partial-onset conditions have been excluded and generalized-onset convulsions are the primary seizure type. Indeed, among patients assigned to arm B of the SANAD trial 63% had IGE and 27% remained unclassified. Among patients with IGE, 26% had JME, 9% had generalized epilepsy with tonic-clonic seizures upon waking, and 37% and an unspecified IGE. The results of the SANAD trial arm B illustrate the factors that should enter into choice of an antiseizure drug for patients with GTC seizures. Overall, valproate and topiramate outperformed lamotrigine for efficacy in terms of time to treatment failure and number of subjects achieving 12-month seizure remission. Valproate widened this efficacy lead over both lamotrigine and topiramate in the setting of idiopathic generalized epilepsy syndromes. But for time to treatment failure due to adverse events, lamotrigine was better tolerated than valproate, and both lamotrigine and valproate were significantly better tolerated than topiramate. In overall cost-effectiveness (cost per quality adjusted life years and cost per seizure avoided) valproate was better than topiramate, and topiramate better than lamotrigine. Women were relatively underrepresented in arm B of SANAD, perhaps attributable to the reluctance of clinicians to expose women of childbearing potential to valproate and again emphasizing that overall efficacy for seizure type is not the only factor to consider when choosing an antiseizure medication. Levetiracetam and zonisamide were not available at the time of the SANAD trial, but in clinical practice are considered by many to be reasonable choices for treating idiopathic or unclassified GTCs, particularly when patient-specific factors, comorbid conditions, or tolerability dictate.

Epilepsy with generalized tonic-clonic seizures only, which includes the epilepsy previously classified as “generalized tonic-clonic seizures on waking,” is an identifiable IGE syndrome. Its exact prevalence is difficult to determine depending on the diagnostic criteria employed. Characteristically, GTC seizures are the sole seizure type, although absence and myoclonic seizures can be a minor component of the syndrome. Alcohol, sleep deprivation, and photic stimulation are strongly provocative. Seizures typically start in the second decade of life but can begin well into adulthood. They occur within an hour of waking in 17%–53% of patients, during wakefulness in 23%–36%, out of sleep in 27%–44%, and without a clear diurnal prevalence in 13%–26%.[125] There is no identifiable structural or symptomatic cause, and the interictal EEG typically shows 4–5 Hz generalized spike-wave complexes. Mutations in a voltage-gated chloride channel gene have been associated with this and other IGEs, and there is often a family history of epilepsy including childhood absence epilepsy (CAE) and JME.[126] The importance of recognizing generalized epilepsy with GTC seizures only lies in choosing a drug regimen that will prevent and not potentially worsen seizures. Valproate and lamotrigine are the most commonly recommended first line drugs, but if these lack complete efficacy or side-effect profiles dictate, levetiracetam, topiramate, or zonisamide are options. The key is to avoid drugs with potential to worsen IGE, including carbamazepine, oxcarbazepine, and phenytoin.

Symptomatic and cryptogenic generalized epilepsies are characterized by generalized-onset seizures, often of multiple types, and associated with underlying structural brain abnormalities, neurologic deficits and clinical encephalopathy. Associated conditions include static encephalopathies and neurodegenerative disorders, and they are the most common type of epilepsies seen in children and adults with intellectual and developmental disabilities (IDD). Diagnostic entities deserving mention in regard to choosing antiseizure drugs for treatment of adults include LGS and progressive myoclonic epilepsy.

Lennox-Gastaut syndrome (LGS) accounts for 1%–4% of all childhood epilepsy cases but 10% of those beginning by the age of 5 years.[127] Although considered a postinfancy epileptic encephalopathy, LGS is also commonly encountered in clinical practice in adults with IDD. Lennox-Gastaut syndrome is defined by characteristic clinical and electrophysiological features: multiple coexisting seizure types that include tonic, atonic, myoclonic, and atypical absence seizures, and an interictal EEG pattern of diffuse slow (<2.5 Hz) spike-wave complexes.[128] Other features supportive of the diagnosis include intellectual and developmental disabilities, treatment resistant seizures, and bursts of generalized fast (10 Hz) EEG spikes during non-REM sleep.[129] Early in the condition, seizures may be tonic-clonic or partial. West syndrome (infantile spasms, encephalopathy, and EEG hypsarrhythmia) precedes LGS in 30%–40% of patients, but about a quarter of children are neurologically normal prior to epilepsy onset.[130,131] Question can be legitimately raised about the value of a diagnostic classification that includes a mixture of cryptogenic and symptomatic causes, uncertain pathophysiology, and occurrence in conjunction with a range of other developmental problems. Lennox-Gastaut syndrome is probably best considered a recognizable territory whose boundaries, however roughly defined, give shape and definition to the broader landscape of symptomatic and encephalopathic generalized epilepsies. Choice of drug treatment for LGS is guided principally by clinical experience, may not match FDA approved indications, and lacks the backing of a strong evidence-based literature of formal comparative studies. Acknowledging the difficulty of seizure control in LGS—a majority of patients continue to have seizures despite treatment— drugs or combinations of drugs should be chosen that are effective against the most frequent or disabling seizure types at the same time taking care to avoid drug-induced sedation that can provoke seizures in LGS. Valproate, with its broad spectrum of action against multiple seizure types, has long been the drug of first choice for children and adults with LGS, appears most effective against myoclonic, atypical absence, and atonic seizures, and may be more effective in cryptogenic than symptomatic LGS.[132,133] Long-acting benzodiazepines such as clonazepam, nitrazepam, and (where available) clobazam are also considered first-line agents for LGS, but their value is often curtailed by side effects or the development of tolerance.[133,134] Impairment of coordination, sedation, paradoxical hyperactivity, and sleep-pattern disturbance associated with benzodiazepines can have negative effects on the quality of life of a patient with preexisting neurologic impairment. Other benzodiazepines, intravenous diazepam, and lorazepam, have been reported to provoke tonic status epilepticus in some patients with LGS.[135] Felbamate, lamotrigine, and topiramate carry FDA indications for treatment of LGS, and their use in the condition is bolstered by placebo-controlled trials.[136–139] Zonisamide and levetiracetam have been reported beneficial in case reports and case series.[140,141] The consequential and often catastrophic seizure frequency and severity associated with LGS has fostered use of alternative and sometimes relatively dangerous treatments. Felbamate is unique among antiseizure drugs in its major action at NMDA receptors and lack of sedative side effects. Its use has been markedly curbed by the associated occurrence of life-threatening aplastic anemia and liver failure, but for patients with LGS whose seizures are severe and refractory to other treatments and who have no history of prior hematologic or hepatic side effects to antiseizure drugs, it represents an efficacious option provided adequate monitoring and close management.[142] Adrenocorticotropic hormone (ACTH) has been used early after the onset of seizures in LGS with some benefit, but with a high relapse rate and multiple complicating systemic side effects.

Avoidance of antiseizure drugs that may worsen seizures in LGS is critical. Although a longstanding treatment among institutionalized patients and patients with IDDs, phenobarbital and other barbiturates can have deleterious effects on behavior in children with LGS, and are associated with seizure-exacerbating sedation. Phenytoin and carbamazepine, while effective against symptomatic partial onset seizures, can exacerbate generalized seizures, and gabapentin may precipitate atypical absence and myoclonic seizures.[143,144]

Progressive myoclonic epilepsies (PMEs) are a group of disorders characterized by myoclonic seizures, tonic-clonic seizures, progressive neurological deterioration, cerebellar signs (ataxia), and dementia. The myoclonic manifestations are fragmentary, multifocal, and in contrast to the myoclonus of IGE, clearly precipitated by posture, action, or sensory stimuli. Progressive myoclonic epilepsy is associated with a variety of disorders, many of which have well-defined genetic bases, but on the whole PME is rare, accounting for less than 1% of all patients with epilepsy. The most common conditions underlying PME are Unverricht-Lundborg disease and Lafora disease. Other causes include mitochondrial encephalopathy with ragged red fibers (MERRF), neuronal ceroid lipofuscinoses (NCL 2, 3 and 4), and sialidosis types I and II. Treatment of seizures in PME is difficult, and seizures remain refractory in many cases. Valproate, alone or in combination with clonazepam, is the most commonly prescribed antiseizure drug in the setting of PME. For patients with mitochondrial diseases (MERRF), valproate is often avoided due to potential interference with carnitine metabolism and association with liver failure.[145] Phenytoin has been reported to markedly worsen seizures and neurologic function in Unverricht-Lundborg disease and should be avoided.[146] In general, any drug with potential to worsen myoclonus in other conditions should be avoided in PME, including carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, and tiagabine.[147,148] Lamotrigine worsens myoclonus less predictably. Adjunctive treatment with levetiracetam, topiramate, and zonisamide have been reported beneficial in PME and may yet prove useful as monotherapy.[149–152]

Choice of Antiseizure Medication: Safety and Tolerability

Adverse side-effect profiles of antiseizure medications

The importance of anticipating, recognizing, and responding to adverse medication side effects derives from the crucial place tolerability inhabits between drug efficacy and drug effectiveness. An efficacious drug will be ineffective if it cannot be taken regularly enough or in high enough doses to control seizures, and the therapeutic window bounded by efficacy and intolerance is often narrow. Following indication for seizure or epilepsy type, tolerability is the next most important factor to weigh in choosing an antiseizure drug or combination of drugs. This is borne out by the witness of patients, a significant proportion of whom report dissatisfaction with their current antiseizure medications, citing problems with energy level, cognition, school performance, childbearing, coordination, and sexual function among others.[153] Approximately 40% of treatment failures in the VA Cooperative Trial comparing carbamazepine, phenobarbital, phenytoin, and primidone for partial seizures were due either to toxicity alone or toxicity in combination with lack of seizure control. Only 5% of patients in this representative study discontinued an antiseizure drug due to lack of efficacy alone.[84] The importance of medication tolerability is further highlighted by its clear relationship to overall quality of life in epilepsy.[154,155]

Adverse effects of antiseizure medications can be divided by organ system and more roughly into those affecting the brain and its function and those affecting some portion of the rest of the body. Further distinction is helpful, and adverse effects can be divided into initiation/titration related, dose related, idiosyncratic, and chronic or delayed effects. Well-known side and adverse effects of antiseizure drugs are listed in Table 3–11 and classified according to this system.

Table 3–11 Common and Serious Adverse Effects of Antiseizure Drugs

Adverse Effects				
Medication	**Dose Introduction**	**Dose Related**	**Chronic Toxicity**	**Idiosyncratic**
Carbamazepine	Nausea/vomiting, headache, sedation/ lethargy, tremor, ataxia, nystagmus, hypersensitivity (rash 10%)	Ataxia, visual disturbance, somnolence/lethargy, tremor	Hyponatremia (dose-related), leucopenia, weight gain, osteoporosis	Aplastic anemia, Stevens Johnson syndrome, SLE, hepatotoxicity
Ethosuximide	Nausea/vomiting, gastric distress, anorexia, diarrhea, drowsiness, insomnia, behavioral changes (children), rash, headaches	GI symptoms, somnolence/ lethargy, insomnia/ irritability	Headaches (persistent), bradykinesia	SLE, blood dyscrasias, lupus-like syndrome, aplastic anemia, hepatotoxicity,
Felbamate	GI disturbance, headache, anorexia, insomnia, dizziness, ataxia	Insomnia, headache, anorexia, excitability	Insomnia, anorexia	Aplastic anemia, liver failure
Gabapentin	Somnolence, dizziness, ataxia, fatigue, headache,	Ataxia, visual disturbance, somnolence, myoclonus	Pedal edema, weight gain	Hallucinations
Lamotrigine	Dizziness, nausea, headache, dyscoordination, tremor, rash (mild 10%; severe 0.3%)	Ataxia, visual disturbance, lethargy somnolence, headache, tics, insomnia		Stevens-Johnson syndrome
Levetiracetam	Fatigue, dyscoordination, behavioral changes (irritability)	Somnolence, dizziness, behavioral changes (irritability)	Mild decreases in RBC/WBC counts	
Oxcarbazepine	Nausea/vomiting, GI distress, somnolence/lethargy, headache, tremor, rash (~3%)	Dizziness, headache, diplopia, ataxia	Hyponatremia (dose-related, esp. in elderly)	Stevens-Johnson syndrome, hepatotoxicity
Phénobarbital	Somnolence/lethargy, dizziness, ataxia, nausea/vomiting, hyperactivity (children)	Lethargy, sedation, dysarthria, ataxia, nystagmus	Cognitive dulling, osteoporosis, Dupuytren contractures, frozen shoulder, joint pain	Agranulocytosis, shoulder-hand syndrome
Phenytoin	Ataxia, incoordination, nausea/ vomiting, somnolence/ lethargy, rash (8.5%)	Ataxia, visual disturbance, somnolence	Gingival hyperplasia, hirsutism, acne, leukopenia, macrocytosis, peripheral neuropathy, cerebellar atrophy, osteoporosis	Stevens-Johnson syndrome, aplastic anemia, hepatotoxicity, pseudolymphoma
Pregabalin	Somnolence, dizziness, ataxia, fatigue, headache	Ataxia, visual disturbance, somnolence	Weight gain	
Tiagabine	Asthenia, nervousness, dizziness, tremor, cognitive dulling, sedation, dizziness, spike-wave stupor (status epilepticus)	Psychosis, insomnia, gait disturbance, shakiness, weakness		
Topiramate	Sedation, ataxia, confusion, memory difficulty, language problems, paresthesias, metabolic acidosis	Slowed thinking, verbal memory disturbance, dizziness, insomnia, paresthesias, anorexia/ anhedonia	Weight loss, kidney stones	Open angle glaucoma, oligohydrosis
Valproate	Nausea/vomiting (severe), sedation (less common), tremor	Ataxia, tremor, visual disturbance, somnolence/ coma	Weight gain, alopecia, leucopenia, thrombocytopenia, coagulopathy (low fibrinogen)	Hepatotoxicity, pancreatitis, hyperammonemia (increased with concurrent topiramate)
Zonisamide	Fatigue, sedation, ataxia, headache, confusion, anorexia, rash (<5%)	Paresthesia, dizziness, anorexia, kidney stones	Weight loss	Stevens-Johnson syndrome, oligohydrosis, kidney stones, psychosis

Initiation and dose-related side effects result from known and even intended pharmacologic mechanisms of the medications. It should be unsurprising that drugs modifying neuronal excitability and firing patterns will have consequences on CNS function beyond controlling seizures. Initiation-related changes in level of arousal, cognition, behavior, mood, and motor coordination are among the most common side effects encountered and vary from agent to agent as well as between individuals taking the same agent. Central nervous system side effects at initiation of treatment are particularly common among patients who are naïve to treatment. Sedation, lethargy, asthenia, visual disturbance, or dyscoordination may occur either irrespective of dose in a pharmacodynamic manner (some patients seem idio-syncratically sensitive to certain drugs) or in a starting dose-dependent manner. Exemplifying the occurrence of side effects with older antiseizure drugs, signs and symptoms of neurotoxicity occurred in approximately 25% of patients started on either carbamazepine or valproate in the VA cooperative trial group 264 with a range of 6%–42% for individual symptoms.[85] A significant proportion of patients develop tolerance to these initial side effects over a matter of weeks. Neurotoxic side effects are more common with faster drug titration schedules than with more gradual approaches to reaching a target dose. This dynamic holds true for even the newer antiseizure drugs, and carbamazepine, levetiracetam, oxcarbazepine, topiramate, and

zonisamide generate less severe effects of initiation toxicity when gradually introduced. When initiation-related side effects emerge, the dose should be reduced and titration slowed. Dose-related side effects are dependent on the total amount of drug taken, similar in quality to those occurring on initiation, and also attributable to the intended or known actions of the drug. Reducing a drug to the last efficacious dose or switching medications is preferable to encouraging patients to tolerate ongoing side effects, recalling that the holy grail of pharmacotherapy in epilepsy rests on three stems: no seizures, no adverse side effects, and optimal quality of life.

Direct comparison of the occurrence of what are often referred to as nuisance or mild but in fact often dose- and efficacy-limiting side effects among drugs is difficult; most of the studies in which tolerability is assessed employ a variety of patient populations, starting doses, titration rates, and target doses. Overall there is a trend toward better tolerability with some of the newer antiseizure medications than with older agents.[156] Among the newer antiseizure medications, direct comparison is again often confounded by trial design, but where reasonable comparisons are available in meta-analysis, levetiracetam and lamotrigine stand out ahead of gabapentin and topiramate in terms of tolerability related retention rates.[157] Ultimately, each person treated for epilepsy represents a statistically significant *n*-of-1 for whom tolerability is a binary affair—side effects on a given drug either occurring or not and either hampering effective treatment or not. As such, and without a well-defined rubric of predictive statistics, choice of drug by potential initiation or dose-related side effects is a matter of educated guesswork—surveying the most commonly encountered side effects associated with individual drugs and reckoning how likely these are to cause distress to a particular patient given his or her particular characteristics. A patient with preexisting balance problems will potentially be less able to tolerate the adverse cerebellar effects of phenytoin. Someone with memory impairment or for whom rapid and accurate retrieval of verbal information is paramount might be expected to be less tolerant of topiramate. And a chronically irascible individual might do best to avoid the potential accentuation of irritability encountered by some patients who take levetiracetam. None of these examples are intended as rigid proscriptions against use of individual drugs in these cases. Rather, they highlight that often the most rational choice of an antiseizure drug we can make in regard to side effect profiles is one that acknowledges patient-specific characteristics and attempts to avoid the most relevant and likely initiation and dose-related side effects.

In an attempt to achieve better seizure control, antiseizure medications are often combined. There is a longstanding belief that, in general, medication side effects of antiseizure drugs are compounded and accentuated by polypharmacy.[158] However, quantitative studies comparing the burden of side effects associated with monotherapy to that of polytherapy challenge this intuition, suggesting that drug load may be as important if not more important than the number of drugs taken in determining the likelihood of neurologic side effects.[159] Drug load can be calculated as the ratio of the prescribed daily dose (PDD) to defined daily dose (DDD), the assumed average effective daily dose for a drug used for its main indication. In a representative study that did not specify which drugs were used, PDD/DDD ratios of <2.0 were associated with an approximately 50%–80% prevalence of neurologic adverse effects regardless of whether patients were on monotherapy or polytherapy regimens.[160] The prevalence of adverse effects increased to 70%–100% for PDD/DDD ratios of >2.0 and to 100% for ratios >4.0, again with no significant difference between monotherapy or polytherapy groups. Caveats pertaining to these results include lack of specificity regarding the polytherapy regimens studied; multidrug treatment may have been specifically designed to avoid additive side effects, or may have been instituted for patients with an initially higher tolerance of adverse effects. Nonetheless, there is data disputing the standard perception that adding antiseizure drugs regardless of dose will compound side effects.

Chronic side effects may not be evident initially, but reflect adverse effects related to long term drug exposure. As listed in Table 3–11, these tend to be drug specific, and are a significant factor in the choice of which antiseizure drug to use. Some, such as weight changes, effects on electrolytes, and gum hypertrophy, are reversible with removal of the offending agent. Others, including phenytoin-related cerebellar atrophy and connective tissue changes with phenobarbital, are enduring.

Serious idiosyncratic reactions to antiseizure drugs

In contrast to drug-related side effects, idiosyncratic reactions are not explained by known drug mechanisms and occur unpredictably in susceptible individuals often without a clear relationship to dosage. Most life-threatening drug effects and those requiring discontinuation of the culprit drug are idiosyncratic, and idiosyncratic reactions to antiseizure drugs are responsible for a majority of fatal drug reactions in children.[161] The three major categories of idiosyncratic reactions are immune-mediated hypersensitivity, general and organotoxicity due to peculiar metabolism, and off-target responses. Although by definition less predictable or dose-related than drug side effects, the risk and consequences of idiosyncratic reactions can be reduced by careful consideration of drug choice and titration in vulnerable subgroups of patients as well as careful monitoring with prompt response to early manifestations.[162]

Rash and mucocutaneous hypersensitivity reactions

Cutaneous manifestations of hypersensitivity ranging from mild to life threatening are the most common idiosyncratic reactions encountered with antiseizure drug treatment. All antiseizure drugs can cause relatively benign skin eruptions. Morbilliform or maculopapular rashes sparing the face and not associated with facial or neck edema occur most often between weeks one and eight of drug initiation. Drug rash is relatively common with aromatic compounds such as carbamazepine, phenytoin, and phenobarbital, with a frequency of 5%–15%.[163] There is a high degree of cross-reactivity among aromatic compounds, with a 40%–60% recurrence of rash when one aromatic antiseizure drug is switched to another.[164] Structurally an analog of carbamazepine, oxcarbazepine is associated with a much lower incidence of hypersensitivity rash, although if rash was encountered on carbamazepine, there is an approximately 30% risk of recurrence on oxcarbazepine.[165,166] The combination of valproate and lamotrigine produces a higher rate of rash than reported with lamotrigine alone, a relationship likely associated with higher starting doses and faster titration schedules of lamotrigine than those currently advised.[167]

Drug-related rash with eosinophilia and systemic symptoms (DRESS) is a severe hypersensitivity reaction characterized by fever, skin eruption, eosinophilia, lymphocytosis, arthralgia, lymphadenopathy, and multiorgan involvement that can include blood dyscrasias, hepatitis, nephritis, myocarditis, thyroiditis, insterstitial pneumonitis, encephalitis, exudative tonsillitis/pharyngitis, oral ulcers, facial edema, hepatosplenomegaly, myopathy, and disseminated intra vascular coagulation.[168] Drug-related rash with eosinophilia and systemic symptoms has been most frequently reported with phenobarbital, phenytoin, and carbamazepine, with several cases occurring on exposure to lamotrigine. Although the systemic involvement of DRESS can be variable, a diffuse maculopapular inflammatory rash and erythroderma are seen in 80%–100% of cases of antiseizure drug-associated DRESS, with fever, eosinophilia, and liver abnormalities the next most common manifestations. The syndrome begins between week 1 and 12 of treatment and resolves with discontinuation of the culprit drug with a favorable outcome in 10%–40% of cases.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, bullous, blistering exanthema with purpura and associated mucosal involvement and skin detachment. Pathophysiologically, these are immune-complement-mediated hypersensitivity reactions. Clinically, they are distinguished by the degree of necrolysis, with SJS defined as <10% skin detachment, TEN as >30% skin detachment, and SJS-TEN overlap syndrome as 10%–30% skin detachment. Leukocytosis is common at onset of the reaction, and later development of neutropenia, lymphopenia, and thrombocytopenia are indicators of poor prognosis.[169] Mucosal involvement is very common in both entities, occurring in approximately 90% of cases. The mortality rate with TEN approaches 40%, whereas for SJS, mortality is <5%. The risk of SJS is highest in the first 60 days of drug exposure.[170] The attention lamotrigine garnered for the occurrence of early postmarketing SJS with fatalities among children and its consequent black box warning possibly diminishes common perception of the risk of severe mucocutaneous hypersensitivity reactions with other antiseizure drugs. The concerning incidence of lamotrigine-induced SJS encountered in its first years of use is likely attributable to higher initial doses and titration rates than currently recommended, as well as its combination with valproate, a potent inhibitor of lamotrigine metabolism. Since careful and conservative revision of dosing and titration schedules for lamotrigine, the incidence of lamotrigine-related SJS has fallen to a rate hard to distinguish from other major antiseizure drugs. Stevens-Johnson syndrome affects between 1 and 10 per 10,000 new users of carbamazepine, lamotrigine, phenytoin, and phenobarbital. To a lesser extent, all of the older antiseizure drugs, and newer agents including felbamate, gabapentin, oxcarbazepine, tiagabine, topiramate, valproate, and zonisamide have been associated with SJS and TEN.[170]

Hepatotoxicity

Antiseizure drug-associated hepatotoxicity can occur as a component of the DRESS system (discussed previously) but also as an organ-specific reaction mediated by immune mechanisms or direct cytotoxicity. Valproate and felbamate raise the greatest concern. Valproate hepatotoxicity has an age-dependent risk of 1:500 in children and between 1:12,000 (polytherapy) and 1:37,000 (monotherapy) in adults.[171] Hepatotoxicity occurs most often in the first three to six months of treatment, and rarely thereafter.

Direct cytotoxicity is believed to be the mechanism of injury for valproate, and intravenous high-dose levocarnitine is indicated as early as possible in emerging cases.[172] Aromatic antiseizure drugs such as carbamazepine, lamotrigine, and phenytoin have also been associated with immune-mediated hepatotoxicity, most often within the context of DRESS. Overall, the incidence of liver failure due to antiseizure drugs has fallen in the past decade due to awareness and avoidance of potentially dangerous drugs in high-risk patients and rapid discontinuation of offending treatments with early symptoms of nausea, vomiting, lethargy, and loss of seizure control.

Pancreatitis

Idiosyncratic hemorrhagic pancreatitis is rarely associated with valproate, and most commonly occurs in the first year of treatment or with dose increases. The combination of abdominal pain, vomiting, anorexia, and high amylase levels should prompt quick discontinuation of valproate, but asymptomatic elevations in amylase have been reported in a significant proportion of patients taking valproate, and in a quarter of children with valproate associated pancreatitis amylase is normal.[173,174] Lipase is a more specific index of valproate-induced pancreatitis.

Hematological reactions

Drug-induced blood dyscrasias result from bone marrow dysfunction and often involve immune reactions. Aplastic anemia is the most serious of these. Among antiseizure drugs associated with aplastic anemia, felbamate has received the most attention, and indeed is the most common culprit with a risk of 1 in 5,000–10,000.[175] Ethosuximide, phenytoin, valproate, and carbamazepine have also been associated with aplastic anemia, the latter with a risk of 1 in 50,000–200,000 patients exposed to the drug.[176] Risk of agranulocytosis, another serious blood dyscrasia, is increased with carbamazepine or phenytoin use. Pseudolymphoma syndrome, a benign dermatological lymphocytic infiltrate with a papular or nodular skin eruption, fever, and lymphadenopathy mimicking lymphoma, is associated with phenytoin and less commonly with other antiseizure drugs.[177] Carbamazepine, phenytoin, lamotrigine, felbamate, primidone, and tiagabine have all been reported in association with idiosyncratic immune mediated thrombocytopenia, while valproate-induced platelet dysfunction and thrombocytopenia occurs in relation to dose.[162] Enzyme-inducing antiseizure drugs can cause folate deficiency related macrocytosis, but in a dose-dependent fashion.

Systemic lupus erythematosis

Systemic lupus erythematosis (SLE) or SLE-like syndromes have been reported on a number of antiseizure drugs, carbamazepine foremost, but including ethosuximide, lamotrigine, phenytoin, valproate, and others.[178,179] Distinctive features of the drug-induced syndrome include lack of symptoms prior to drug exposure, remission with drug discontinuation, and high antihistone antibody titers.[180] The symptoms themselves are difficult to distinguish from idiopathic SLE and can occur many years after initiation of the culprit drug.

Ocular reactions

Rare acute angle-closure glaucoma can occur with topiramate.[181] Blurring of vision, the earliest symptom, is reversible with immediate discontinuation of the drug. Milder acute onset myopia has also been associated with topiramate use. Any visual changes should prompt ophthalmologic evaluation and consideration of switching to another antiseizure drug.

Laboratory monitoring and prevention of adverse reactions

Clinical evaluation is the foundation of efficacy and safety monitoring when treating epilepsy. But concern about idiosyncratic reactions and effects, which by definition are difficult to clinically predict, has driven recommendations for routine, scheduled laboratory surveillance for aberrations in interval drug levels, hematology, and serum chemistry data. The rationale behind these recommendations is that routine laboratory monitoring will allow detection and interception of reactions before they become serious or life threatening. But to what extent is this notion established in evidence and what is its source? Documentation of the occurrence of serious or dangerous drug effects accumulates during drug trials and is archived in common references such as the *Physician's Desk Reference* and others. Postmarketing surveillance and published reports sometimes result in revision of these compendia of untoward drug potentials. Included in this literature are reports of the accompanying laboratory anomalies, the quantifiable and recognizable footprints of the disorders in question. But little in this process suggests that screening laboratory data will detect clinical events before they arrive, that scanning for footprints will lead to the crook before the crime is committed. In fact, a fair body of literature suggests that routine laboratory screening fails to provide preemptory information, and if made the basis for clinical decisions—a change in drug or switch to another—can possibly result in harm if seizure control is compromised.[182] There is also an enormous cost generated by routine laboratory monitoring in asymptomatic patients. In what circumstances and for whom then should blood be drawn to detect the potential of drug-related disease in patients with epilepsy? In short: before a drug is started, when there is suspicion that prior adverse events will repeat themselves, in response to clinical changes suggestive of new events, in patients at higher risk of a reaction, and those whose ability to communicate subtle symptoms and signs is impaired.

Other measures may decrease the likelihood of serious adverse events, and are patient and drug specific. Children with inborn errors of metabolism are predisposed to drug-related hepatotoxicity, and valproate in particular may be contraindicated.[183] A history of allergy to one medication (e.g., phenytoin) raises the likelihood of cross sensitivity to similarly structured aromatic compounds, and antiseizure drugs with low allergenic potential (gabapentin, levetiracetam, pregabalin, topiramate, valproate, and zonisamide) should be preferred when there is a history of serious hypersensitivity reactions. Informed patients and available clinicians reduce the risk that early signs of serious reactions will be missed. Careful patient education about potential reactions and their herald symptoms can inform prompt clinical follow up for evaluation.

Management of side effects and serious reactions

Any serious reaction or reasonably suspected serious reaction warrants discontinuation of the most likely causative drug. Since ongoing antiseizure treatment is usually required to prevent worsening of the patient's condition, a substitute antiseizure drug is usually necessary. Available agents with low allergenic potential are listed previously, but also include benzodiazepines, whose sedative effects may temporarily be offset by the benefit of shortterm seizure control. Drugs that can be titrated quickly, such as levetiracetam, gabapentin, and to a lesser degree zonisamide, are reasonable alternatives.

Diagnosis requires a broad approach since many idiosyncratic reactions affect multiple organ systems, and complete blood counts, a comprehensive metabolic panel, and thyroid function tests are indicated. Additional immunologic assays should be performed where appropriate to the clinical syndrome.

Direct management of hypersensitivity reactions is controversial and lacks the backing of controlled clinical trials, but the use of corticosteroids (prednisone 0.5–2.0 mg/kg/d) is practiced by most clinicians. Serious reactions such as SJS and TEN are best managed in a burn center where appropriate wound and ancillary care can be provided.

Patients with mild hypersensitivity reactions can be rechallenged with the suspected culprit drug if necessary to prove a definitive association. The rationale behind this exercise is that of establishing a clear relationship in order to avoid unnecessary avoidance of a potentially useful drug or group of drugs, as well as reintroducing a drug that was shown clinically useful. In the case of nonserious hypersensitivity reactions, rechallenges should be performed with lower starting doses and slower titration schedules, and even in the case of lamotrigine have been shown successful.[184]

Choice of Antiseizure Medication: Pharmacokinetic Profile

General principles of pharmacokinetics

Efficacy and tolerability of antiseizure drugs are closely dose-dependent and level-dependent, necessitating careful consideration of how much of a particular agent is

administered and how often to achieve a stable therapeutic but nontoxic level. An antiseizure drug takes a long journey before arriving at its intended destination in the CNS, and the physiologic variables interposed along that route govern its pharmacokinetic characteristics (Table 3–12).

Table 3–12 Pharmacokinetic Parameters of Antiepileptic Drugs*

					Elimination Route (%)				
Drug	**Bioavailability**	**Vol. of Distribution (L/kg)**	**Protein Binding (%)**	**$t_{1/2}$ (h)**	**Renal**	**Liver**	**Maintenance Dose (mg/kg/d Unless Otherwise Specified)**	**Dosing Interval**	**Therapeutic Range (µg/mL)**
Carbamazepine	75–85%	0.8	75	9–15	1	99	10–25	bid-tid	4–12
Clonazepam	>80%	3.0	85	20–60	<5	>90	0.03–0.3	bid	5–70 Ng/mL
Clorazepate		1.2	97	50–100	<5	>90	0.5–1.0	bid	0.5–1.9 Ng/mL
Ethosuximide	93%	0.7	<9	30–60	<20	>80	15–40	qd	40–100
F elbamate	>90%	0.8	25	13–22	50	50	15–60	bid-tid	30–100
Gabapentin	Dose-dependent	0.7	0	5–7	100	0	1800–3600 mg/d	tid	4–8
Lamotrigine	98%	1.0	55	12–62	10	90	300–500 mg/d	bid	3–14
Levetiracetam	100%	0.5–0.7	<10	6–8	100	0	1000–3000 mg/d	bid	20–60
Oxcarbazepine	70%	0.8	40	9	1	99	1200–2400 mg/d	bid	5–50
Phénobarbital	>90%	0.6	45	75–110	25	75	1–1	qd	10–40
Phenytoin	70–100% variable by manufacturer	0.8	90	9–36	5	95	4–7	qd, bid	10–20
Pregabalin	>90%	0.5	0	6	90		150–600 mg/d	bid-tid	Not established
Primidone	>90%	0.7	0–20	10–15	40	60	10–20	tid	5–15
Tiagabine	~90%	1.4	96	7–9	2	98	32–56 mg/d	bid-qid	5–70
Topiramate	80%	0.7	15	12–24	65	35	200–800 mg/d	bid	2–25
Valproate	90% (81–89% delayed release)	0.2	70–93	6–18	2	98	10–60	bid-tid (qd for ER form)	50–150
Zonisamide	100%	1.5	40	63	35	65	100–600 mg/d	qd	15–40

* Normal values for adults on monotherapy; pediatric dosages may vary

qd = once a day; bid = twice a day; tid = three times a day; qid = four times a day

BIOAVAILABILITY

Bioavailability expresses the proportion of a drug that reaches systemic vascular circulation after its introduction to the body, and is determined by absorption. An intravenously administered drug is 100% bioavailable by definition and provides the reference by which oral bioavailability is measured. The bioavailability of orally administered drugs is affected by their formulation and preparation, gastric acidity, bowel absorption and motility, gastrointestinal blood flow, and coadministered medications and food. Bioavailability of most antiseizure drugs is a static, linear proportion of dose. Gabapentin is unique in its dose-dependent bioavailablity through a saturable L-amino acid transporter system. Sixty-eight percent of a 300 mg dose of gabapentin reaches the systemic circulation, but only 46% of a 1200 mg dose and 35% of a 1600 mg dose given twice a day are bioavailable.[185] The bioavailability of antiseizure drugs sometimes depends on concomitantly ingested medications and food. For instance, phenytoin's solubility is highly affected by pH, and its rate and extent of absorption are decreased in the presence of calcium or ammonium salt antacids, as well as by coadministration with enteral feeding preparations.

The rate of absorption of a number of antiseizure drugs is intentionally slowed by extended release formulations with the goal of producing a more shallow dose to peak concentration curve and thereby decreasing the peak (and potentially toxic) levels required to maintain an adequately therapeutic trough. The principles of this strategy are illustrated in Figure **3–5**, which depicts the conceptual fluctuation of drugs levels throughout the day of an immediate versus extended release formulation. By providing a more graded absorption curve, extended release formulations allow more drug overall to be given, potentially enhancing efficacy without sacrificing tolerability. This theory is borne out in practice, where tolerability and effectiveness are improved by use of a sustained or extended release preparation.[186] In general, extended release formulations are recommended where available, and also have the advantage of reducing the frequency of doses needed to produce a therapeutic response, and with a simplified schedule, reduce the likelihood of nonadherence to a drug regimen.

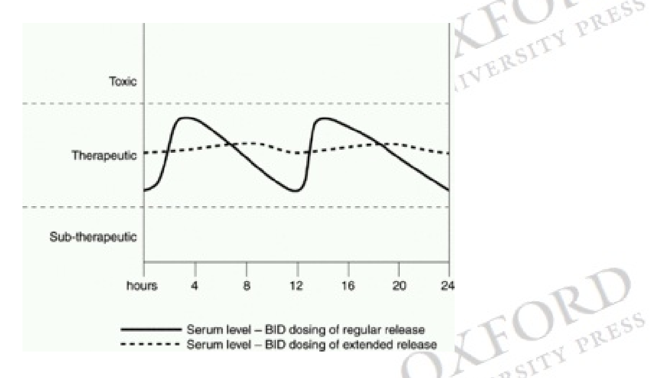


Figure 3–5.
Extended release drug formulations minimize fluctuation in serum levels. By providing a more sustained and gradual delivery of drug, they decrease the likelihood that toxic or near toxic peak doses will be required to sustain efficacious levels over time.

When measuring antiseizure serum levels, the rate of absorption needs to be considered. The trough level of an enteric coated drug such as valproate will not occur just prior to the next dose given, but rather some time before levels rise from the most recent dose, in this case approximately two to three hours later. Additionally, the overall bioavailability of an individual agent may vary depending on its formulation. Extended release valproate requires a dose 8%–20% higher than that of the regular or delayed release formulation to achieve the same approximate effective level.

An important issue related to antiseizure drug absorption and bioavailability is the bioequivalence of brand and generic formulations. The FDA requires that the 90% confidence interval (CI) of the ratio of a generic to reference compound for area under the drug concentrationtime curve (AUC) and maximum concentration (Cmax) remain within an 80%–125% range.[187] For antiseizure drugs, where efficacy and toxicity are often bound to a narrow therapeutic window, the need for reliable serum levels at a given dose over time raises concern that switching from brand to generic forms or among generic manufacturers might result in loss of seizure control or development of unexpected side effects. Conceptually, a drug whose effective and safe concentration for a given patient at a given dose lies on either edge of the therapeutic window could verge well outside that window after a change in formulation even while satisfying the FDA definition of equivalence. A mostly anecdotal literature documents unpredictable and adverse clinical consequences resulting from switches in antiseizure drug formulation, but obviously does not include the large number of uneventful transitions.[188] Patients perceive the risk generated by a change in drug formulation as a real concern, 10%–14% of whom when surveyed report encountering clinically significant problems following a switch from brand to generic antiseizure drugs.[189,190] Of surveyed neurologists, 65%–68% report having patients who experienced breakthrough seizures and 56% report emergence of adverse side effects.[191,192] Similarly, 33% of surveyed neurologists reported breakthrough seizures and 27% reported problems with tolerability when switching *among* generic formulations. For individual patients who encounter problems, the cost of injury, emergency medical evaluation, hospitalization, and work lost easily outstrips the savings generated by switching to less expensive generics. Yet without more conclusive epidemiological data, the overall cost-effectiveness of generics on the scale of health care systems remains to be demonstrated or disproved, and financial pressures continue to drive switching to generic antiseizure drugs when available. Until we gain a more accurate and comprehensive understanding of the scope and extent of this issue, steps can be taken to minimize the risk to patients. The American Academy of Neurology's (AAN) position statement on coverage of anticonvulsants for patients with epilepsy highlights the need for prescribing decisions to remain in the hands of physicians and their patients, and opposes the substitution of antiseizure drugs without the attending physician's approval.[193] Out of interest for patient safety, generics should not be substituted for brand or switched among manufacturers by pharmacies without the patient and physician being informed. There are several situations that provide good reason to avoid and oppose switching from a drug demonstrated safe and effective to an untried generic. If a patient with difficult to control seizures has demonstrated a narrow therapeutic response to an existing regimen and consequences of breakthrough seizures would be dire (serious injury, loss of employment, or drivers license), the reduction in immediate cost likely does not warrant the potential risk associated with switching to a generic. In some cases, dose equivalence cannot be achieved with available generic products, and similarly, extended, sustained, delayed, and immediate release formulations are often not interchangeable. If there is reasonable expectation that a generic formulation will be equally effective and less costly, careful surveillance of serum levels may be a strategy to avoid untoward consequences of switching. Once a stable, safe, and effective baseline drug level is established for an individual patient, this can be compared to steady state levels of the substituted formulation sampled at least five halflives into the new regimen, and repeated again for reassurance. Discrepancies in properties of absorption and bioavailability between products can then be addressed with dose adjustment. Heightened vigilance for development of new side effects should accompany any change in medications, including switching between formulations where changes in bioavailability may be clinically significant.

Protein binding

The extent of plasma protein binding is an additional determinant of how much drug is delivered to the CNS relative to a given dose. Many antiseizure drugs are bound to plasma proteins to some degree, and only their free, unbound fraction is available for passage across the blood brain barrier (BBB). Protein binding becomes clinically important when the bound fraction of a drug is high, as is the case with phenytoin and tiagabine and to a lesser degree with valproate and carbamazepine. The free phenytoin level is roughly 10% of the total serum level, but increases if displaced by drugs that compete for binding sites, when total protein levels are low (hypoalbuminemia), or when protein binding is deranged (renal dysfunction). For instance, an ostensibly nontoxic total phenytoin level of 20 μg/mL will yield a free level of 3 μg/mL, well outside the normal range of 1.0–2.0 if protein binding of phenytoin is reduced even moderately to 85% due to displacement by a drug such as valproate. Other medications, including acetazolamide, high doses of salicylic acid, phenylbutazone, ceftriaxone, nafcillin, and sulfamethoxazole, compete with phenytoin for protein binding and may have a clinically significant effect on free phenytoin levels if given concomitantly.[194] Protein binding becomes consequential in the setting of serious illness where protein binding is impaired, such as in the case of renal dysfunction. Where there is potential for significant divergence from normal free to total serum level ratios, free levels should be obtained to more accurately assess the actual bioavailability of drug, and may not correspond predictably to total serum levels. Calculated adjustment of the free drug fraction relative to albumin levels, while they may seem an elegant solution to the problem of free-total level mismatches, do not adequately account for the derangement in protein binding that occurs in serious illness, and particularly in the setting of hepatic or renal dysfunction.[195,196] The pharmacokinetics of drugs with lower protein bound fractions are significantly less affected by competition for protein binding. The free fraction of valproate varies relative to its total level due to saturable protein binding kinetics at therapeutic concentrations, going from 7% at 50mg/dL to 15% at 100mg/dL to 30% at 150mg/dL.197 Thus, incremental rises in total valproate serum levels result in nonlinear increases in the free fraction available for passage into the CNS. Since as the free fraction rises, metabolism of valproate rises proportionally, total valproate levels have a curvilinear relationship to dose at drug levels above 50 mg/dL.[198] Drugs such as aspirin or naproxen that compete for protein binding can elevate the free fraction of valproate.[199]

Volume of distribution

In addition to protein binding, which effectively takes a certain amount of drug out of the available pool for passage into the CNS, antiseizure medications are distributed to other tissues and fluids before reaching equilibrium. Lipid solubility of a drug determines how fast it is transported across biologic membranes, and in obese patients may increase the volume of distribution for a given drug. The volume of distribution (Vd) is a theoretical expression of the relevant volume in which an amount of drug would need to be uniformly distributed to produce an observed blood concentration and is described in terms of L/kg. The Vd of a particular drug provides a clinically useful variable for calculating the loading dose required to achieve a target serum level: Loading dose (mg) = Vd (L/kg) × ΔC (target level-current level in mg/L) × weight (kg).

Elimination and metabolism

As soon as they are introduced to the bloodstream, drugs begin to leave by transformation in the liver, excretion from the kidneys, or both. The rapidity of this process determines how quickly a drug will have to be replaced to attain a desirable concentration. For most antiseizure drugs, this process has a linear relationship to dose, meaning, for instance, that the drug will be removed twice as quickly if the concentration is doubled. Nonlinear kinetics come into play when transport or metabolic functions are saturable. Phenytoin demonstrates nonlinear, saturable kinetics, and particularly at higher doses (approaching 8 mg/kg per day in adults) increases in dose cause disproportionate increases in levels. Another important concept related to elimination is that of steady state. Since only a portion of a repetitively dosed drug is eliminated for any given dose over a period of time, levels gradually rise with subsequent doses. Eventually, a steady state is achieved wherein daily elimination of drug matches the daily dose. With regular dosing, 97% of steady state concentration is reached after five elimination half-lives of a drug. Hence, a change in drug dosing will require at least five half-lives at a constant, regularly administered dose before its effect on therapy or levels can be accurately assessed.

Most antiseizure medications are partially or completely eliminated by hepatic metabolism. Their roles as substrates for and influences on hepatic enzymes highly influence their pharmacokinetics, and particularly so when taken in combination (Table 3–13). The principle metabolic reactions are catalyzed by the cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes. Several isoenzymes relevant to hepatic metabolism of antiseizure drugs include CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A4. Of these, CYP3A4 has the least substrate specificity, and is the most abundant in the liver. As a substrate for specific isoenzymes, an antiseizure drug's elimination rate, and thereby serum concentration at a constant dose, can be altered by exogenous and endogenous substrates that either induce or inhibit isoenzyme activity. And antiseizure drugs, due to enzyme inducting or inhibiting properties of their own, can alter the clearance rate of other compounds. Major antiseizure drug-drug interactions are listed in Table 3–14. In addition to these, several special circumstances deserve mention. Carbamazepine is unique among antiseizure drugs for inducing its own metabolism. The process of carbamazepine autoinduction takes place over two to six weeks, increasing clearance by shortening its half-life and lowering serum levels.[200–202] As a result, response to an initial dose of carbamazepine may diminish over a short period of time, and the dose-level curve is decrementally curvilinear rather than linear. Certain antiseizure drugs undergo hepatic metabolism to pharmacologically active compounds, knowledge of which can be important for predicting and monitoring clinical effects. For instance, primidone is metabolized in the liver to phenobarbital and phenylethylmalonamide (PEMA), both of which have their own antiseizure and neurotoxic properties. Coadministration of primidone and hepatic enzyme inducers such as phenytoin or carbamazepine preferentially speeds biotransformation to phenobarbital, effectively lowering primidone levels while raising those of phenobarbital even to the point of toxicity. Carbamazepine is metabolized by the P450 system to carbamazepine-10–11-epoxide (CBZ-E), a compound active against seizures and believed responsible for many of carbamazepines toxic side effects. The normal adult ratio of CBZ-E to carbamazepine of 10%–15% increases toward 20% during pregnancy and is higher in childhood. In the setting of inducers of carbamazepine metabolism, and in the presence of a concomitant inhibitor of epoxide hydrolase such as valproate, the CBZ-E to carbamazepine ratio approaches 50%, potentially leading to excessive toxicity even at relatively low doses and moderate levels of carbamazepine itself.[203] Levels ofCBZ-E should always be checked alongside those of carbamazepine when assessing possible toxicity. A similar dynamic occurs when carbamazepine is given along with either primidone or felbamate (Table 3–14).

Table 3–13 Hepatic Metabolism of Antiseizure Drugs

	Hepatic Isoenzyme					
	CYP-450					
Drug	1A2	2C8	2C9	2C19	3A4	UGT
Carbamazepine	▨ ▲	▨	▨ ▲	▲	■ ▲	▲
Phenytoin	▲	▨	■ ▲	▨ ▲	▲	▲
Phenobarbital	▲	▲	■ ▲	▨ ▲	▲	▲
Ethosuximide		▨	▨		■	
Valproate			▨ ▽	▨		■ ▽
Oxcarbazepine				▽	▲	■
Lamotrigine						■ ▲
Lorazepam						■
Midazolam					■	
Diazepam				■		
Felbamate				▽	■ ▲	
Tiagabine					■	
Zonisamide					■	
Topiramate				▽	▲*	

Hepatic metabolic pathway substrates:
■ = major, ▨ = minor

Effect on isoenzyme:
▲ = induces; ▽ = inhibits

UGT = UDP-glucuronosyltransferase

*Dose-dependent

Table 3–14 Significant Antiseizure Drug-Drug Interactions

Drugs		
A	**B**	**Interaction**
(enzyme inducers) Carbamazepine, Phenytoin, Phenobartbital	(enzyme-dependent clearance) Lamotrigine, Topiramate, Tiagabine, Valproate, Oxcarbazepine	Enzyme-inducers in column A significantly increase clearance (↓ half-life) of those in column B, reducing their concentration to as little as 50% and sometimes necessitating compensatory increases in the dose of B. Discontinuation of a concomitant inducer (column A) can result in marked rises in the concentration of drugs in column B
Valproate	Lamotrigine	VPA competes with LTG for glucuronidation, inhibiting LTG metabolism, and increasing its concentration by a factor of 2 or more, often necessitating reduction of LTG's dose. The risk of serious rash with LTG introduction is increased with higher initial doses or rapid titration. If LTG is added to VPA, the initial dose of LTG should be lower and titration schedule slower than if added to an enzyme inducer or noncompetitor.
Phenytoin	Valproate	Interaction is complex: VPA displaces PHT from protein binding sites and inhibits PHT metabolism. In practice, total PHT concentration tends to decrease with unchanged concentration of the free (unbound) PHT fraction. Follow free PHT levels.
Carbamazepine	Valproate	VPA preferentially inhibits metabolism of carbamapepine-10–11-epoxide (CBZ-E), the CBZ metabolite believed responsible for most of CBZ's side effects. Significant ataxia, nausea/vomiting, and lethargy can result. Check CBZ-10–11-epoxide levels.
Phenobarbital	Valproate	VPA inhibits CYP2C9 metabolism of PB, increasing PB concentration, sometimes to the point of toxicity. PB dose may need to be reduced.
Phenobarbital	Carbamazepine	PB induces CBZ metabolism, reducing CBZ concentrations.
Primidone	Carbamazepine	Induction of CBZ metabolism and relative sparing of CBZ-E metabolism resulting in reduced efficacy and increased toxicity of CBZ.
Carbamazepine	Lamotrigine	Pharmacodynamic interaction of uncertain mechanism may result in neurotoxicity (sedation, dizziness, dulled cognition). For reasons that are unclear (i.e., CBZ-E is not increased), toxic side effects improve with reduction of CBZ even when addition of LTG precipitated their onset.
Phenytoin	Topiramate, Oxcarbazepine	Inhibition of CYP2C19 by TPM or OXC occasionally results in toxic increases in PHT concentration that necessitate adjustment of PHT dose.
Ethosuximide	Valproate	VPA sometimes increases ESM concentration. ESM sometimes decreases VPA concentration.
Phenobarbital	Phenytoin	PB and PHT compete for the same site of metabolism, inhibiting each other's metabolism. Low doses of PB induce PHT metabolism, but higher doses inhibit PHT metabolism in an unpredictable interaction that necessitates closely monitoring the level of both agents.
Felbamate	Carbamazepine, Phenobarbital, Phenytoin, Valproate	FBM decreases VPA clearance, increasing VPA concentrations by ~50%. FBM inhibits metabolism of PB, PHT, and VPA, significantly increasing their plasma concentration and often necessitating dose reduction of these agents to avoid toxicity. FBM reduces CBZ concentration but raises concentration of the CBZ-E metabolite, simultaneously decreasing efficacy and increasing toxicity of CBZ.

This table does not represent a complete list of interactions and interactions may not occur in all patients on these combinations.

A great number of non-antiseizure medications influence hepatic metabolism of antiseizure drugs and thus can have in impact on their effectiveness or toxicity. Conversely, antiseizure medications can have a clinically significant impact on the effectiveness or toxicity of other medications. Tables 3–15 and 3–16 list a number of the most clinically significant pharmacokinetic interactions between antiseizure and other drugs. Notably, there are many drugs that inhibit CYP3A4 and thus can surreptitiously raise levels of drugs such as carbamazepine. Similarly, enzyme-inducing antiseizure drugs, of which carbamazepine, phenobarbital, and phenytoin are the chief actors, increase the metabolism and clearance of many other medications. Several interactions deserve particular attention and reflect commonly encountered or serious interactions.

Table 3–15 Significant Effects of Other Drugs on Antiseizure Drugs

Drugs		
Antiseizure	**Drugs Other**	**Interaction**
Carbamazepine	(macrolide antibiotics) Erythromycin Clarithromycin	Macrolides inhibit the CYP3A4 isoenzyme, resulting in decreased clearance of CBZ and potentially toxic increases in its concentration. Avoidance of the offending antibiotics is easier (and safer) than making transient and unpredictable adjustment of the antiseizure medication.
Phenytoin	Trimethoprim/ Sulfamethoxazole (Bactrim)	Inhibition of PHT metabolism with possible development of PHT toxicity. Synergistic alteration of folate metabolism increases risk of megaloblastic anemia.
Phenytoin	Fluconazole, Itraconazole, Ketoconazole, Miconazole	Inhibition of PHT metabolism with possible development of PHT toxicity. If needed for long term antifungal treatment, reduce PHT dose if and as symptoms of toxicity emerge.
Carbamazepine, Phenytoin	Fluoxetine	Fluoxetine inhibition of CBZ and PHT can result in significant rises in their concentration, associated toxicity, and necessitate dose reduction of antiseizure medication.
Lamotrigine	Sertraline	Sertraline inhibits UGT metabolism of LTG, potentially resulting in toxic concentrations. Adjust LTG accordingly.
(enzyme-inducing) Carbamazepine, Phenobarbital, Phenytoin	Tricyclic antidepressants (TCAs)	Complex interaction: TCA concentration is decreased and antiseizure drug concentration is increased resulting in reduced TCA efficacy and increased antiseizure drug toxicity.
Carbamazepine, Phenytoin	St. John's wort	St. John's wort may increase metabolism of CBZ and PHT, reducing their efficacy.
Phenytoin	Cimetidine Omeprazole	Cimetidine and omeprazole may inhibit PHT metabolism. Reduce dose of PHT if symptoms of toxicity develop.
Carbamazepine	Propoxyphene	Propoxyphene significantly inhibits CBZ metabolism, potentially increasing CBZ levels toward toxicity.
Carbamazepine, Phenytoin	Diltiazem Verapamil	Some inhibition of CBZ and PHT metabolism by diltiazem or verapamil may result in elevation of CBZ or PHT levels.
Lamictal	Oral contraceptives	Oral contraceptives can lower LTG concentrations by induction of LTG metabolism. Dose adjustment may be necessary.
Carbamazepine, Gabapentin, Phenobarbital, Phenytoin	Calcium-based antacids	Gut absorption of some antiseizure drugs is reduced by coadministration with antacids, particularly so for PHT.

This table does not represent a complete list of interactions and interactions may not occur in all patients on these combinations.

Table 3–16 Significant Effects of Antiseizure Drugs on Other Drugs

Drugs		
Antiseizure	**Other**	**Interaction**
(Enzyme-inducing) Carbamazepine, Felbamate, Phenobarbital, Phenytoin, Oxcarbazepine, Topiramate	Oral contraceptives (OCPs)	Enzyme-inducing antiseizure medications significantly increase the metabolism of OCPs, reducing their effectiveness and raising the risk of unwanted pregnancy. OCP formulation needs to be adjusted in response to addition of or addition to an enzyme-inducing antiseizure drug.
Carbamazepine, Phenobarbital, Phenytoin	Benzodiazepines	Benzodiazepine metabolism is induced by enzyme-inducing antiseizure drugs, reducing effectiveness and sometimes necessitating dose adjustment.
Carbamazepine, Phenobarbital, Phenytoin	Haloperido, Risperidone, Quetiapine	Enzyme-inducing antiseizure drugs increase the clearance of some antipsychotics, potentially decreasing their effectiveness.
Carbamazepine, Phenobarbital, Phenytoin	Theophylline	Increased metabolism of theophylline reduces its effectiveness.
Carbamazepine, Phenobarbital, Phenytoin	Warfarin	Induction of warfarin metabolism by antiseizure drugs can cause a drop in INR, and potentially life-threatening loss of anticoagulant activity. With discontinuation of an enzyme inducer, there is risk of warfarin toxicity/hemorrhage.
Phenytoin, Topiramate	Digoxin	PHT and TPM induce digoxin metabolism, decreasing effectiveness.
Phenytoin	Amiodarone	Amiodarone levels are reduced by addition of PHT, and amiodarone inhibits CYP2C19 metabolism of PHT
Carbamazepine, Phenobarbital, Phenytoin	(HMG)-CoA reductase inhibitors	Addition of an enzyme-inducing antiseizure medication may increase the rate of metabolism leading to inadequate treatment of hypercholesterolemia if doses are not adjusted.
Carbamazepine, Phenobarbital, Phenytoin	Corticosteroids	Increased metabolism of corticosteroids reduces their therapeutic effectiveness and may necessitate dose adjustment.
Carbamazepine, Phenobarbital, Phenytoin	Antivirals metabolized by CYP3A4	Accelerated antiviral metabolism in the presence of enzyme-inducing antiseizure drugs can result in reduced efficacy mimicking inconsistent treatment with development of viral resistance.
Carbamazepine, Phenobarbital, Phenytoin	Cyclosporin	Accelerated cyclosporine metabolism in the presence of enzyme-inducing antiseizure drugs may result in loss of immunosuppressant activity.
Phenytoin, Tiagabine, Valproate	Aspirin, NSAIDs	Drugs that compete for protein binding can displace highly protein bound antiseizure drugs, causing elevation of their free (pharmacologically active) fraction. Free levels should be assessed if there is any question of a mismatch between total levels and apparent efficacy or toxicity.

This table does not represent a complete list of interactions and interactions may not occur in all patients on these combinations.

Macrolide antibiotics are commonly prescribed, as is carbamazepine. Yet the potential interaction between erythromycin or clarithromycin and carbamazepine often goes unconsidered, likely because these drugs are usually prescribed by different clinicians. Macrolides inhibit CYP3A metabolism of carbamazepine, reducing its clearance and potentially leading to toxic concentrations. Development of acute carbamazepine toxicity after initiation of macrolide treatment is well-documented.[204,205] Second-generation antiseizure drugs are less problematic in this regard. Propoxyphene, either alone or in combination with acetaminophen, inhibits carbamazepine metabolism, and symptoms that might be taken for evidence of narcotic sensitivity or overdose may actually indicate carbamazepine toxicity.

Antidepressants are frequently prescribed drugs, and are certainly warranted in the setting of epilepsy, where there is an increased prevalence of depression. Important interactions occur between antiseizure drugs and some of the most commonly prescribed antidepressants. These interactions don't preclude the safe and effective use of psychotropic drugs for patients with seizures, but dictate careful monitoring and adjustment of dosages in certain circumstances. Tricyclic antidepressants (TCAs), increasingly prescribed for indications such as headache and chronic pain, undergo P450 metabolism, and their plasma concentration can be reduced by enzyme inducers (carbamazepine, phenobarbital, phenytoin). Working the other direction, TCAs such as nortriptyline, imiprimine, and trazadone can also inhibit the metabolism of antiseizure medications.[206] Newer antidepressants, fluoxetine in particular, inhibit multiple isoenzymes, and coadministration can raise antiseizure drug levels to the point of toxicity. Fluoxetine-carbamazepine and sertraline-lamotrigine combinations account for the most common antidepressant-antiseizure drug interactions.[207,208]

The interaction of antiseizure drugs with oral contraceptives (OCs) can be consequential. Endogenous estrogen and its fluctuations can influence the clearance of drugs, although with the exception of its effect on lamotrigine, not to a clinically significant degree. However, OCs depend on reliable levels of exogenous hormonal steroids for effect, and enzyme-inducing antiseizure drugs can accelerate hepatic metabolism of contraceptives, reducing their efficacy, and increasing the risk for unwanted pregnancy. This is particularly so for low-dose estrogen formulations. Any woman of childbearing age taking a strongly enzyme-inducing antiseizure medication should be queried about birth control. Increases of the estrogen dose of OCs to >50 μg are advisable, as is the use of a secondary method of contraception.[209] Although felbamate, oxcarbazepine, and topiramate are weak inducers of hepatic enzymes, the potential consequence of contraceptive failure commends OC dose adjustment and use of a secondary barrier method with these agents as well.

Treatment with warfarin is another situation where interactions with other drugs can have critical consequences. Metabolized primarily via CYP2C9, with some involvement of CYP3A4 and CYP1A2, warfarin is sensitive to the enzyme-inducing effects of carbamazepine, phenobarbital, or phenytoin, and anticoagulant activity needs to be monitored carefully with appropriate warfarin dose adjustments if these drugs are added or discontinued. Newer antiseizure drugs do not appear to affect warfarin's metabolism to a significant degree.

These lists are by no means complete, including the most commonly encountered interactions. Their number highlights the need to cross-check any new addition to a patient's drug regimen for potential pharmacokinetic interactions. They also point to the relatively few significant interactions encountered with newer antiseizure drugs.

Hepatic and renal dysfunction require careful attention to mechanisms of drug pharmacokinetics. In addition to loss of hepatocytes and altered liver blood flow with impairment of drug metabolism, liver disease can cause hypoalbuminemia and reduction in albumin binding affinity that affects protein binding. Since the extent of liver disease can be difficult to quantify, drugs with low protein binding and that require minimal metabolism by liver enzymes for elimination are preferable. These include gabapentin, levetiracetam, pregabalin, and topiramate. The availability of an intravenous formulation of levetiracetam makes this an attractive option for patients too ill to take drugs by mouth. Renal dysfunction is more readily quantified by measurement of creatinine clearance. Prescribing information for antiseizure drugs that are extensively renally excreted includes guidelines for dose reduction in the setting of kidney disease. For patients on hemodialysis, supplemental doses of water soluble low-protein-bound compounds such as gabapentin, levetiracetam, phenobarbital, or topiramate immediately following dialysis are recommended.[210] Derangement of protein binding affinity that occurs in renal disease can affect the free fraction of highly protein drugs such as phenytoin and valproate.

Pharmacogenetics and antiseizure drug metabolism

Despite attempts to predict and quantify the therapeutic and toxic dose response to an antiseizure drug based on experimental observations and established parameters, there is often significant interindividual variability. Genetic differences in the biochemical processes of metabolism are a factor contributing to this unpredictability. Drugs that undergo metabolism via the cytochrome P450 system are subject to interindividual genetic variations in the makeup of the relevant enzymes. A patient may be an extensive or poor metabolizer of a given drug depending on which alleles for a given enzyme he or she possesses. There are 13 identified alleles of the CYP2C9 gene, 15 alleles of the CYP2C19 gene, and 39 variants of the CYP3A4 gene.[211] The distribution of these variants in combinations that confer P450 enzyme activity ranging from supranormal to subnormal roughly falls along ethnic lines. In the scope of this chapter, discussion of specific genetic polymorphisms is less important than recognition of the potential contribution of genetic factors to the disposition of antiseizure drugs; not all patients who experience toxicity at moderate doses are mismanaging their medications, and not all those who fail to experience efficacy at higher doses are nonadherent to treatment. Whether genetic metabolic profiling will find a place of clinical relevance for predicting response to medications remains to be demonstrated. For instance, the identified genetic variations of CYP2C9 and CYP2C19 that confer clinically significant loss of enzymatic activity and elevation of phenytoin levels occur in less than 1% of Caucasians and ~10% of Asians.212,213

Laboratory monitoring of antiseizure drug levels

In light of the pharmacokinetic variables interposed between a drug's entry into the body and its availability for passage into the CNS, methods to ascertain how much drug is being seen by its intended target in relationship to a given dose can be useful if properly employed. Namely, measurement of serum drug concentration provides a relatively direct assessment of the likelihood that a safe and effective dose is being administered. As with any tool, the utility of antiseizure drug laboratory monitoring depends on the task to which it is applied. Recommended reference ranges for antiseizure drug concentrations are established on the basis of populations of patients with epilepsy, many of whom have refractory seizures and are maintained on more than one antiseizure medication, but generally reflect the range of nontoxic and effective levels for a majority of patients.[214] Crucial to the rational use of drug levels is the concept that underlies their establishment: that the effective concentration of an antiseizure drug is that which provides efficacy without undue adverse side effects or toxicity. The effective concentration is thus defined clinically, and in many patients may be apparent based on clinical criteria even without drawing blood. The importance of this distinction between clinical and laboratory monitoring of antiseizure drug effectiveness lies in avoiding the temptation to dose a drug according to a predefined serum level target instead of its clinical effect. For instance, many patients with relatively mild epilepsy can be adequately maintained on drugs at levels below the recommended range, and some have suggested that the concept of a lower limit of established serum concentration ranges be abandoned.[215] Conversely, many patients can be maintained at ostensibly supratherapeutic levels if needed to control seizures without development of adverse side effects, and discovery of a concentration above the recommended range should not prompt dose reduction in a patient who is otherwise stable. In short, antiseizure drugs should be titrated to efficacy and avoidance of toxicity and not adjusted by the numbers in most situations. The recommended therapeutic ranges for older and newer antiseizure drugs are listed in Table 3–17. For older drugs, these ranges have more clinical value than for newer agents, whose therapeutic windows are wider and less well-established.

Table 3–17 Antiseizure Drug Therapeutic Serum Ranges and Value of Assay

Older Antiseizure Drugs			**Newer Antiseizure Drugs**		
Drug	**Range (μg/mL)**	**Comments**	**Drug**	**Range (μg/mL)**	**Comments**
Carbamaze-pine	4–12	Valuable; T_{max} varies by form	Felbamate	30–100	Potentially valuable
CBZ-E	0.2–2.2	Valuable as an assay of CBZ toxicity	Gabapentin	4–8	Limited value
Clonazepam	5–70*	Limited value	Lamotrigine	3–14	Potentially valuable
Ethosuximide	40–100	Valuable	Levetiracetam	20–60	Limited value
Phenobarbital	10–40	Valuable	Oxcarbazepine	5–50	Potentially valuable; Measured as 10-monohydroxy derivative (MHD) metabolite
Phenytoin	10–20	Valuable	Pregabalin	—	Levels not established
Primidone	5–15	Monitor PB levels	Tiagabine	5–70	Potentially valuable
Valproate	50–150	Valuable; Tmax varies by form	Topiramate	2–25	Potentially valuable
			Zonisamide	15–40	Potentially valuable

* (Ng/mL).

T_{max} = time to peak level after dose.

CBZ-E = Carbamazepine-10–11-epoxide.

When the question of whether routine sampling of antiseizure drug levels improves outcomes has been formally investigated, the results suggest not. Three randomized trials comparing groups of patients whose management was guided by regularly obtained drug levels to groups managed by clinical monitoring alone (levels were not sampled or clinicians were blinded to laboratory results) demonstrated either no difference in seizure control and side effects or a tendency toward higher rates of toxicity when dosing decisions were dictated by drug levels.[216–218] One review of these studies concluded that there is no good evidence to support routine drug level monitoring in stable asymptomatic patients.[182] Despite the demonstrated inability of drug level monitoring to supplant clinical assessment of effectiveness or toxicity, there are specific circumstances where measuring drug levels, while not absolutely required, may be clinically useful.

- *After initiation of a new treatment*. nce steady state conditions have been established (~5 half-lives into treatment with a stable dose), drug levels should be correlated with dose. This provides a reference point or baseline for future adjustments if needed in response to treatment failure, development of side effects, or the addition or withdrawal of concomitant medications that influence drug concentrations.
- *In children to adjust for growth*. Changes in body mass and age-related changes in clearance rates require periodic reevaluation of dosing to maintain efficacy that can be based on interval serum drug levels.
- *In response to apparent lack of efficacy*. Before entertaining switching to or adding an additional agent, drug levels can be useful to assess the likelihood that dose increases are necessary or to detect unexpectedly low concentrations.
- *In response to development of side effects*. Adverse side effects at relatively low levels of one drug may help predict the development of similar events on drugs with similar mechanisms of action.
- *To assess the relative contribution or lack of contribution to either efficacy or tolerability of individual drugs in multidrug regimens*. If more than one antiseizure drug is being prescribed and there is incomplete efficacy or development of side effects, drug level monitoring may reveal which is most likely the underdosed or excessively dosed agent. Serum levels in this case provide a rational basis for choosing which medication to adjust.
- *Upon addition or withdrawal of a concomitant medication that may affect levels, and to assess the accuracy of dose adjustments performed in response*. Hepatic enzyme induction or inhibition of susceptible drugs may take several weeks to manifest, and appropriately timed reassessment of levels can guide dose adjustments as well as evaluate the cause for emerging treatment failure or apparent toxicity.
- *During serious illness*. Liver or kidney dysfunction can significantly alter antiseizure drug pharmacokinetics, including metabolism and protein binding, and frequent serial measurement of total and free levels (where relevant) can guide dose adjustments to ensure stable control of seizures in the setting of medical instability.
- *During pregnancy*. Lamotrigine levels undergo significant fluctuation in response to changes in endogenous hormones, and frequent routine serum level monitoring is required in order to adjust dosage accordingly. Drugs should be kept at the lowest effective levels (established on a patient-specific basis) needed to control seizures and minimize dose-related teratogenic effects. Free and unbound levels of highly protein bound drugs may also fluctuate and should be monitored when possible.
- *To assess adherence to a drug regimen*. Undetectable or extremely low levels of a drug may indicate that it is not being taken as prescribed.
- *To calculate an estimation of the loading dose required to rapidly correct apparently subtherapeutic drug levels. See the previous discussion of volume of distribution* (V_d).

Accurate assessment of serum drug levels requires knowledge of individual drug formulation pharmacokinetics. And useful assessment requires careful timing of drug level sampling in relation to the pertinent clinical question. For most drugs, a steady state concentration at a given dose is achieved after five half-lives, and serum levels sampled before that point poorly reflect the ultimate dose-to-level relationship. After dose initiation or a change in dose, assessment of a baseline level can be performed relatively quickly for drugs with short half-lives, whereas drugs with long half-lives will require a longer interval before steady state levels can be accurately ascertained (i.e., within two days on a consistent dose of levetiracetam versus three weeks for phenobarbital). If the question in mind is that of efficacy, and recognizing that established reference ranges are based on trough levels, the serum level should be drawn at a time in relationship to daily dosing when it is most likely at its nadir. Most often this is just prior to the first morning dose, but for drugs with a delayed release or enteric coated preparation, it may actually be a few hours after the last dose taken. If potential toxicity is being evaluated, the level should be drawn at a time when it is most likely at its peak as reflected by the time to maximum level per dose (T_{max}) for that drug. The T_{max} for an individual drug varies considerably according to formulation, shorter for immediate release forms and longer for delayed or extended release. In any of these situations, repeated or comparison levels should be sampled under consistent conditions and in a consistent relationship to dosing.

The use of a total drug level as guide for treatment decisions assumes that this accurately reflects the amount of pharmacologically available drug in the bloodstream. For drugs that are highly protein bound (phenytoin, tiagabine, and to a lesser degree valproate), this assumption may not always be valid, and as described previously, even relatively minor displacement from their binding sites may result in clinically significant alteration in the pharmacologically active free fraction. For these reasons, whenever there is a suspicion deranged or altered protein binding, free levels should be compared to total levels, and if there is deviation from the expected ratio, free levels should then be followed. Circumstances that warrant checking or following free levels include coadministration of medications that compete for protein binding sites, pregnancy, hypoalbuminemia, or hepatic or renal dysfunction.[219–222]

Influence of pharmacokinetic profile on choice of an antiseizure drug

Ease of use is an important factor to consider when choosing an antiseizure drug. For clinicians the ideal drug is one with a wide therapeutic index, relatively uncomplicated titration schedule, predictable dose to response relationship, and few or no significant drug-drug interactions. A major advantage commending newer antiseizure medications in place of older ones is their relative paucity of significant pharmacokinetic drug-drug interactions and predictable, linear kinetics. Lack of interactions facilitates ease of transition to or addition of another medication if a first choice proves ineffective. Additionally, the risk of interactions attendant to the addition or removal of non-antiseizure medications, many of which the prescribing clinician may have little initial control over, is reduced if there are fewer potential interactions to begin with. Predictable kinetics are also an advantage of newer antiseizure medications, requiring less dose individualization and reducing the need for routine drug level monitoring.[223] Rapidity of onset may also be an important factor. Most titration schedules are dictated by the avoidance of initiation and titration-related side effects, and a long delay between dose initiation and achievement of a reasonable target dose places patients at risk of recurrent seizures in the interim. Levetiracetam and zonisamide have the advantage of demonstrated efficacy at starting doses.

The relative simplicity of a taking a drug is important to patients as well, and inconsistent adherence to a treatment regimen is a major contributor to the occurrence of breakthrough seizures.[224] Drug regimen adherence diminishes with multidose regimens, decreasing from ~80% for dosing once or twice a day, down to 70% for dosing twice a day, and 40% for dosing four times a day.[225] Thus there is an obvious advantage to drugs that can be taken in two divided daily doses at most. Additionally, long-acting formulations (those most likely to be dosed twice a day or once a day) have been shown to reduce the occurrence of peak dose side effects at the total daily doses required for seizure control. Where adherence to a regimen has proven a significant impediment to efficacy, drugs with long half-lives that can reasonably be given once a day (zonisamide, Depakote ER) should be considered.

Monotherapy is preferred for initial treatment of epilepsy, and one drug, gradually increased in dose toward experience of either seizure freedom or development of enduring, objectionable side effects, is effective for a majority of patients. Once selected on the basis of efficacy for seizure or epilepsy type, safety and tolerability profile, pharmacokinetics, and patient characteristics, dosing and titration requirements for individual drugs must be considered. Regrettably, many antiseizure drugs are expensive, and tiered stratification of copayments or the availability of generic formulations may necessarily intrude on consideration of which is the best available drug in a given circumstance. Initial dosing and titration recommendations are available from a variety of sources, but as highlighted previously, dosing is an individualized affair, and some patients may experience efficacy at lower than recommended doses while others may experience a good response at doses higher than recommended without undue side effects.

Continuing and Revising Treatment

If after a reasonable trial of an antiseizure drug, seizures are not controlled, a change in treatment will be necessary. But should the next drug be added to or replace current treatment? Behind this practical question lie further questions that press the limits of what we understand about the pharmacodynamic properties of antiseizure drugs. And the answer to this practical question stands with one foot planted in demonstrable evidence and the other more in theoretical supposition. We do know that poor response to a first or second drug predicts poor response to the next. Two key studies following treatment response of newly diagnosed epilepsy illustrate this point, showing that after failed monotherapy with two antiseizure drugs, the likelihood of seizure freedom on a third or combination of drugs falls dramatically.[226,84] Approximately 60% of patients with epilepsy become seizure free with moderate doses of a first or second drug. Of these, 5%–10% will later relapse and remain difficult to control.[227,228] The remaining 30%–40% have seizures that are difficult to control and likely were so at the outset. Attempts to treat seizures refractory to the first two drugs tried with a third drug or combination of drugs is successful in only a small fraction of patients.[226] These are often patients who have a higher seizure density prior to treatment, likely reflecting the severity of their underlying condition. In addition to seizure frequency, epilepsy type plays a role in pharmacoresistance. Symptomatic/cryptogenic generalized epilepsies are more difficult to treat than symptomatic partial-onset epilepsies, and both more so than idiopathic generalized epilepsies.[229,230]

These established facts influence the consensus practice of epileptologists, a majority of whom follow a stepwise approach to treatment that begins with sequential monotherapy with at least two drugs before considering drug combinations. After that, ~30% proceed to drug combinations for IGE and nearly 50% for localization-related epilepsy.[231] Less clear is whether certain combinations of drugs have demonstrable advantages over others in terms of efficacy.

Approximately 20% of clinicians begin evaluation for epilepsy surgery if two monotherapy drugs fail to control complex partial seizures, and ~35% do so after inefficacy of an initial combination of drugs. Work up for epilepsy surgery requires the resources of an epilepsy center to identify a functional or structural lesion, establish a confident localization of seizure onset, and evaluate whether that region can be surgically resected without significant loss of function. Refinement of temporal lobectomy/hippocampectomy procedures has dramatically improved the outlook for medically refractory temporal lobe epilepsy. A less invasive surgical alternative, insertion of a vagus nerve stimulator (VNS), may reduce the frequency or severity of seizures in some cases. The responsive neurostimulator (RNS), a device designed to detect local epileptic electrical patterns and deliver an abortive pulse of stimulation, is under investigation and may prove a good option for patients with focal-onset seizures in regions that cannot be approached with resective surgery. Any surgical procedure carries risk, and consideration of these, including VNS, should be preceded by thorough evaluation to ensure accurate diagnosis and identification of seizures and seizure types.

Polytherapy principles

Rational polytherapy is an intuitively attractive concept, the notion that drugs with complementary mechanisms of action can be combined to achieve efficacy exceeding that of either drug alone and without additive side effects. This idea rests on the dubious supposition that we know and can predict a drug's clinically relevant action and on an uncertain knowledge of the pertinent pathophysiology of epilepsy in individual patients. To make sense of how antiseizure medications work, they are often divided into three major mechanistic categories: drugs that modulate excitatory voltage-gated ion channels, drugs that enhance GABAergic inhibition, and drugs that diminish glutaminergic neurotransmission. This classification allows a rough matching of drug target to seizure type. Drugs that block sodium channels are generally considered effective for patients with partial-onset and generalized tonic-clonic seizures, and those with a broader spectrum of action for patients with multiples seizure types. Yet drug efficacy can be difficult to predict on the basis of mechanism and sometimes confounds expectations. For instance, absence seizures often respond to lamotrigine but can be worsened by other sodium channel blockers. Similarly some GABAergic agents suppress absences (clonazepam) and others exacerbate them (phenobarbital). Patient heterogeneity within established classification schemes also contributes to unpredictable medication effects. Within groups of patients with clinically similar partial-onset seizures who fail treatment with a sodium channel blocker, some respond to the addition of a GABAergic drug, while others do not.[232] This likely reflects differences in underlying pathophysiologic processes that are not disclosed by clinical presentation. The conceptual precision of rational polypharmacy is limited by our inexact understanding of how seizure drugs work and of the condition they intend to treat. Yet within these constraints, there appear to be combinations of drugs that are more beneficial than others, although the evidence is not strong.[233] There also may be pharmacodynamically problematic combinations.

In principle, combining a sodium channel blocker with one that enhances GABAergic effects should be a good strategy, approaching the imbalance of neuronal excitation and inhibition from both sides. Indeed this appears to be the case, and low doses of phenobarbital improve efficacy when added to phenytoin.[234] The combination of lamotrigine and valproate appears more efficacious than lamotrigine combined with either phenytoin or carbamazepine for partial-onset and tonic-clonic seizures.[235] And when either lamotrigine or valproate fail to control seizures alone, combination can improve efficacy.[236] Whether this favorable effect is due to pharmacodynamic synergy or a pharmacokinetic interaction is not entirely clear. The dose of lamotrigine should be reduced by approximately 50% if valproate is added due to hepatic enzyme inhibition by valproate; if added to valproate, lamotrigine should be started at a lower dose and titrated more slowly. A combination of ethosuximide and valproate may be beneficial if either of these alone fail to control absence seizures.[237] Combination therapy with lamotrigine and topiramate appears efficacious for a wide range of seizure types.[238] In general there is growing evidence that the broad range of newer antiseizure medications, many of which have novel or distinguishing mechanisms and minimal adverse drug-drug interactions, provide opportunities for efficacious and well-tolerated combinations that may improve the outlook for treatment response when initial therapy fails.[239]

The list of possible antiseizure drug combinations that might provide additive or synergistic efficacy has not been exhausted nor has the relative benefit of one combination over another been carefully assessed in many cases. Extrapolating from these observations, a reasonable approach to polypharmacy, perhaps more rationalized than rational, involves the following principles.[240]

- Combine medications that independently are considered efficacious for the identified seizure type or epilepsy syndrome.
- Combine medications with disparate mechanisms of action, and avoid combinations with nearly identical mechanisms.
- Combine medications with disparate side effect profiles to avoid additive adverse effects.
- Combine medications with a low potential for metabolic interactions.
- If an added drug completely controls seizures, it is possibly efficacious alone, and slow withdrawal of the first should be considered.
- Avoid overly sedating combinations (e.g., two GABAergic agents) due to the risk of exacerbating seizures by promoting excessive drowsiness.

Recognition of limitations in our knowledge of how and when putative antiseizure drug mechanisms matter, and incomplete understanding of the pathophysiology of seizures in individual patients should temper the notion of predicting ideal medication combinations for patients who fail initial therapy. But lacking more specific evidence-based guidance for polytherapy, applying principles of complementary drug targets, steering clear of adverse drug-drug interactions, and taking a stepwise approach to medication trials remain the best available tools for treating seizures that have already proven difficult to treat.

Deciding to stop antiseizure treatment

The natural history of untreated epilepsy suggests that some patients may not need to be treated indefinitely. Overall, for patients who have been seizure free on treatment for two or more years, seizure relapse rates after antiseizure drug withdrawal are estimated to be 25% at one year and 29% at two years, with a range of 12%–67%.[241] The timing and occurrence of relapse after gradual antiseizure drug withdrawal over six months has been analyzed in a large randomized prospective trial.[242] At two years, 41% of the treatment withdrawal group had relapsed compared to 22% in the group that continued treatment. Relapses occurred most often in the first months of treatment discontinuation, 50% during medication tapering, and 50% soon thereafter. Attempts to identify which patients are more or less likely to successfully discontinue treatment weighing factors that include etiology, seizure type, epilepsy syndrome, age at onset, duration of epilepsy, number of seizures, and EEG features have produced mixed results, but several principles appear to hold true across a range of studies.

Individuals with remote symptomatic epilepsy (epilepsy from a remote but identifiable cause or event), ongoing neurological deficits or developmental disabilities have seizures

harder to control than those whose seizures are cryptogenic or idiopathic. If controlled on treatment, remote symptomatic epilepsy carries a higher risk of recurrence after treatment is discontinued.[243,244,241]

Specific seizure types do not consistently correlate with risk of recurrence, and are better understood as markers of underlying epilepsy syndromes, some of which strongly predict whether longstanding treatment will be necessary. For instance, multiple seizure types are seen in symptomatic/cryptogenic generalized epilepsy syndromes and carry a poor prognosis for remission off treatment.[245] In contrast to seizure types, specific epilepsy syndromes confer relatively definitive prognoses for remission.

Benign rolandic epilepsy (BRE) carries an excellent prognosis for complete remission in nearly 100% of patients despite the persistence of characteristic EEG abnormalities.[246] A majority of patients with childhood absence epilepsy remain in remission after discontinuing antiseizure drugs provided the diagnosis is accurate and there are no coexisting seizure types.[247] The occurrence of generalized tonic-clonic seizures in addition to absences reduces remission rates from 78% to 35%.[248] Approximately 15% of children with absence seizures go on to have JME, a syndrome with far less favorable remission rates.[249] Juvenile myoclonic epilepsy responds well to appropriate treatment, but relapses in nearly 100% of patients who attempt to discontinue antiseizure drugs.[247]

Duration of seizure freedom on treatment has some influence on the likelihood of successful treatment discontinuation. Most studies of treatment discontinuation recruit patients who have been seizure free for at least two years. Potential for relapse is similar among patients who are seizure free for two- or four-year intervals but higher in patients with a seizure-free interval of only one year.[77]

Ongoing EEG abnormalities might seem a logical marker of ongoing epileptogenic potential, portending a poor chance of seizure freedom if treatment is discontinued. But the evidence for this is conflicting and depends on the patient's age. Numerous studies of children have shown that EEG abnormalities of multiple kinds, not only epileptiform discharges, decrease the likelihood that treatment can successfully be withdrawn, but are more predictive of outcomes in children with cryptogenic epilepsy than remote symptomatic epilepsy.[77] There is a relative paucity of information regarding EEG and prognosis for relapse in adults, and the available results are mixed. On review, there appears to be an association between persistent EEG abnormalities and a modest increase in recurrence risk.[241,250,251] Yet an abnormal EEG does not definitively preclude the possibility of seizure freedom after discontinuation of treatment.

The number of seizures, history of status epilepticus, duration of seizures, and number of drugs required to achieve seizure freedom are surrogate measures of epilepsy severity and confer varying risk of recurrence after treatment is stopped.[241] A multivariate analysis of risk factors for relapse performed in 1993 combined the most predictive of these prognostic indicators in order to develop a calculable index of recurrence.[252] The weighted factors included age at epilepsy onset, refractoriness after initiating treatment and number of antiseizure drugs (markers of severity), history of tonic-clonic or myoclonic seizures (epilepsy syndrome markers), duration of seizure freedom on treatment, and EEG abnormalities. The resulting prognostic index represents a practical way to calculate odds of seizure recurrence at one and two years after discontinuation of treatment (Table 3–18). Interestingly, 95% CIs for actual relapse rates compared to index-predicted rates were narrower in groups calculated to have lower risk of seizure recurrence suggesting that the model may be more accurately predictive where it matters most. This index was validated only within the study with a group of patients not included in initial data collection, and like similar predictive models has yet to undergo more rigorous external validation.[252]

Table 3–18 Prognostic Index of Seizure Recurrence After Withdrawal of Antiseizure Drugs[252]

Factor	**Value to be added to score**
1. Starting score for all patients	−175
Age >16 years	45
Taking more than one antiseizure drug	50
Seizures occurring after the start of treatment	35
History of any tonic-clonicseizures (generalized-orpartial-onset)	35
History of myoclonic seizures	50
EEG while in remission:	
Not done	15
Abnormal	20
Duration of seizure-free period (years = D)	200/D
2. Total score	T
3. Divide T by 100 and exponentiate	$Z = e^{T/100}$
Probability of Seizure Recurrence	
On continued treatment	
1 year	$1 - 0.89^Z$
2 year	$1 - 0.79^Z$
On slow withdrawal of treatment	
1 year	$1 - 0.69^Z$
2 year	$1 - 0.60^Z$







Beyond seizure and epilepsy characteristics, risks and benefits pertinent to the individual must be weighed. Direct medical and physical risks are a concern probably more highly perceived than warranted. The notion that if seizures recur, they will do so dramatically in the form of status epilepticus is not borne out by data. Among patients who have never experienced status epilepticus, and who were well controlled when taking medications, the risk of status epilepticus after antiseizure drug withdrawal is low.[253] The risk of serious injury associated with epilepsy is a function of seizure frequency, and also quite low in the setting of single seizure.[254] Rather, psychosocial issues are likely the weightiest for adults considering discontinuing medications. For an independent adult who is driving, seizure relapse can cause serious adverse social and economic consequences. Indeed, during enrolment in the largest prospective trial of antiseizure drug discontinuation to date, the proportion of patients who held a driver's license was notably higher in the group who declined to participate.[252] Among those who did consent to participate, psychosocial measures in areas of perception of stigma and restriction in the group that discontinued treatment were better than in the group that stayed on antiseizure drugs.[255] Ongoing drug treatment carries its own psychosocial burden even among patients who are seizure free.

Patients for whom withdrawal of treatment is deemed reasonable should be counseled about the potential risks, and many clinicians advise curtailing potentially dangerous activities such as driving during medication tapering and for a period of approximately three to six months after. With the exception of barbiturates and benzodiazepines, for which longer tapering schedules are required to avoid provoking withdrawal seizures, there is no compelling evidence that the rate of drug withdrawal affects the likelihood of seizure recurrence.[256] To the contrary, excessively prolonged tapering regimens may only serve to lengthen the duration of uncertainty as well as the activity restrictions that often accompany medication discontinuation plans. Depending on patient disposition and the relative risks involved, tapering a drug to discontinuation can safely be accomplished over the course of several weeks. Should seizures recur after a trial off of medications, there is good reason to believe that control of seizures will return to its previous level once appropriate treatment is reinstituted.[256]

Special considerations in epilepsy pharmacotherapy

Women and Pregnancy

The issues for women with epilepsy are manifold. As for men, efficacy is at the core of a high quality of life. Women who wish to have children are confronted with additional challenges because their fertility may be less than that of women without epilepsy, antiseizure drugs may pose risks for the developing baby, and guidelines regarding breast-feeding are awaiting a more firm evidence base. The topic deserves a monograph of its own that would encompass related concerns, such as bone health (discussed in the following section). Here, we outline the major issues and suggest therapeutic approaches.

Epilepsy may affect the regularity of menstrual cycles and fertility.[257] This can occur in any epilepsy type but appears more common in temporal lobe epilepsy.[258] Related to this is the increased risk of polycystic ovarian syndrome (PCOS), which has as its clinical features cystic ovaries, obesity, hirsutism as a sign of increased androgen to estrogen levels (or LH/FSH >2), and the aforementioned menstrual irregularities. There is an associated increased risk of diabetes, cardiovascular disease, and endometrial cancer. While the increased risk of PCOS appears related to epilepsy, it may be related also to medications, particularly valproate,[259–261] although there are data to the contrary.[262,263] Since valproate increases weight in some individuals, this could be a contributing factor. The net result is a reduction in fertility,[264] which could be exacerbated by CYP450-inducing drugs that can lower the level of circulating hormones.

Some women have a catamenial pattern to their seizures with an increased risk of breakthrough seizures in midcycle or at menses.[265–267] This occurs at these times because progesterone, which has a relatively anticonvulsant effect on the GABA-A receptor, is low relative to estrogen, which has a relatively proconvulsant effect.

Management of birth control may be complicated also. Many drugs lower the level of hormones, whether endogenous or exogenous, in the form of OC agents. Among the drugs that lower OC effectiveness are phenytoin, carbamazepine, oxcarbazepine, the barbiturates, primidone, topiramate, and felbamate. For women taking these agents, an OC with at least 50 µg estrogen is recommended. Lamotrigine does not affect the level of circulating hormones, but estrogens may increase the clearance of lamotrigine, dropping its level roughly in half. For women taking lamotrigine and an OC (or during pregnancy, as estrogen levels rise), the lamotrigine level will be lower and may require closer monitoring. Conversely, during the week of the menstrual cycle during which no estrogen is administered, lamotrigine levels will rise, with an increased likelihood of adverse effects. This will require tailoring the dosage of medication carefully to avoid toxicity during the placebo week of the OC cycle and avoid seizures during the weeks receiving estrogen. Many specialists suggest progesterone-based birth control, reasoning that it will, if anything, have an anticonvulsant effect, and would not interact as estrogens do with lamotrigine.

Pregnancy presents additional considerations. Managing seizures is particularly important since seizures during pregnancy, especially convulsive seizures, could injure the developing baby due to hypoxia or trauma. Exposure of the fetus to antiseizure drugs carries risks as well. Pregnancy registries have been invaluable resources to help guide treatment during pregnancy, and we urge all practitioners to suggest to their patients that they participate in one or more registries. Some, like the North American Registry based in Boston, are interested in women with epilepsy whatever their treatment; others are for women taking only specific drugs.

The risk of major malformations is a serious concern when considering treatment during pregnancy (registries typically do not have enough patients enrolled to comment on minor or rare malformations for individual drugs). The North American Registry reported a baseline rate of 1.8% of major malformations in the community compared to a rate approaching 3% in women with epilepsy.[268] The rate increased with more antiseizure drugs, and the rate of any malformation was nearly 30% in women taking two or more antiseizure drugs. Carbamazepine and phenobarbital, of the older drugs, have appeared to be relatively safe in terms of major malformations with risks of ~5%. Phenytoin carries a slightly higher risk of ~9%.[269] Valproate, by contrast, has been linked to a nearly sevenfold increase in relative risk of major malformations[270] as well as with lower verbal IQ scores tested several years after birth.[271] The UK registry has confirmed these findings and reported in addition a dose-dependent increase in major malformations for lamotrigine, an effect that was relatively modest—an increase to 5.5% from 3.5% in untreated women with epilepsy[272]—but which has not been replicated across other registries.[273] Finally, there is an increased risk of isolated cleft lip or palate in children exposed to lamotrigine, reported from the North American Registry. This effect is significant, increasing the risk approximately 20-fold, although the overall risk still remains low. Newer drugs have not amassed enough data to provide similar results. Ongoing data collection assures that findings will be available in the future.

At present, what can be safely recommended? Pregnancy planning should begin well in advance of conception and discussions about pregnancy should occur with any woman of child-bearing age, with content that is age-appropriate and tailored to the individual. The drug regimen should be as simple as possible and still compatible with a high likelihood of continued seizure control. Care should be taken to review the risks and benefits of each medication, with the understanding that it may take time to switch to a regimen with a more acceptable risk profile. Most epileptologists recommend dietary supplementation with 5 mg daily of folic acid, although an evidence base is lacking regarding the necessary dosages or the efficacy in countering any drug-induced malformation. The final decision must take into account the likely outcomes measured against the risk tolerability of the patient. For example, while the rates of major malformations with valproate may approach 12%,[270] if this were the only medication that was known to control seizures, this might be an acceptable risk (88% chance of no major malformation) for some women.

Recommendations regarding lactation and breast-feeding are harder to establish. Those drugs that have little or no protein binding are likely to be present in breast milk, whereas strongly protein-bound drugs (tiagabine, phenytoin, valproate) do not accumulate.[274] Breast-feeding has clear benefits, but there has been little study of the effects of exposure to the infant, particularly if there had been prenatal exposure. An assessment based on known benefits and relatively unknown risks may turn on the risk tolerability of the mother. While some drugs, such as barbiturates and topiramate, may have cognitive adverse effects in children or adults, the effects on infants have been less well studied.

Bone Health

Bone health is attracting increasing attention as an important factor in quality of life for persons with epilepsy. Fractures carry significant morbidity and occur at an increased rate in persons with epilepsy.[275–279] In part, this may be due to an increase of risk factors in the epilepsy population (Table 3–19), including a more sedentary lifestyle, fewer

outdoor activities with less exposure to sun, and a greater propensity to trauma, if only due to seizures. However, it is also true that a number of drugs used to treat seizures increase the rate of bone loss and thus increase the rate of fractures;[280] it is not surprising, therefore, that persons with epilepsy or those who take antiseizure drugs are more likely to have thin bones.[281,282]

Table 3–19 Risk Factors for Osteopenia and Osteoporosis

Age	Family History of Osteoporosis	Ethnicity (Caucasian or Asian)	Poor Nutrition
Small frame	Menopause	Smoking history	Alcohol use
Hyperthyroidism	Hyperparathyroidism	Liver disease	Medication use: Glucocorticoids; Heparin

Bone density increases until the third decade of life, stabilizes, and then begins to decline in the sixth decade. Since treatment for epilepsy is in many cases life-long, one of the challenges, apart from controlling seizures, is to tailor a regimen so that peak bone density is reached and then maintained. Managing the lifestyle factors (exercise, diet, cessation from smoking, moderate alcohol consumption, etc) is necessary, but part of the process is to choose medications that, wherever possible, will not hamper bone health. Ongoing challenges exist. Past studies have been hampered by the lack of good controls for factors other than medication. Our knowledge of what constitutes normal vitamin D levels (and therefore the appropriate intake from diet) has evolved toward higher levels. These have confounded studies whose aims have included determining the effect of antiseizure medications on bone and, equally important, the effect of treatment. Many antiseizure medications simply have not been studied.

The most common drugs used to treat epilepsy that are known to reduce bone density are those that induce the metabolism via the cytochrome P450 system, phenytoin, primidone, and phenobarbital.[283–285,282] However, induction of vitamin D metabolism may not be the exclusive mechanism, because there is conflicting evidence for a deleterious effect on bone by carbamazepine, another CYP450 inducing drug. Ultrasonography and dual-emission X-ray absorbtiometry (DEXA) scans may show a reduced thickness of bone, but fracture rates are only slightly increased.[284,286–291] Similar results have been shown for valproate.[283–284,292–294] For drugs released more recently, there are scant data on bone density, and of the many possible alternative mechanisms by which bone density could be reduced—blocking absorption of calcium, reduced bone deposition or enhanced resorption, hyperparathyroidism—none has been shown to definitively occur in association with antiseizure drug use.

What actions are appropriate at this time? In persons with increased risk factors (Table 3–19), or those who have taken drugs known to decrease bone density, it is prudent to suggest a bone density scan and supplementation of the diet with calcium and vitamin D. As of the time this chapter was written, 600 mg of calcium twice daily, and vitamin D, 400–1000 IU twice daily, is reasonable. The guidelines for adequate supplementation are continuously reassessed, however. If reduced bone density is present, higher doses of vitamin D may be required, up to 5–15,000 IU daily; in such circumstances, a referral to a bone endocrinologist is usually indicated, with consideration of other therapies such as bisphosphonates. Recognizing, however, that such drugs rarely allow complete repletion of bone mass, the key to successful maintenance of bone health is prevention.

Treatment of Epilepsy in the Elderly

The most rapidly growing segment of the population in the United States is also the group with the highest incidence of epilepsy, exceeding that of children.[295] Common causes of adult-onset epilepsy—cerebrovascular disease, tumors, and Alzheimer's disease—increase in incidence with aging. Ischemic and hemorrhagic stroke is the leading cause of seizures in this population, and is associated with a high incidence of status epilepticus, with seizures occurring more often in the setting of large, hemorrhagic, or cortical infarcts.[296–298] Yet recognition of seizures is confounded by in increase in look-alike conditions among the elderly, including metabolic disturbance, transient ischemic attacks, syncope, cardiac arrhythmia, and fluctuating dementia.[299,300] These other causes of spells in the elderly raise the potential for underdiagnosis of epilepsy. In a retrospective chart review of 159 elderly patients with late-onset seizures, the average delay in diagnosis was 1.7 years, most often because patients did not seek evaluation.[301] Only 20% of patients with complex partial seizures in this review were diagnosed immediately, and seizures were frequently mistaken for cardiac events or transient ischemic attacks (TIAs). Attentive clinical history and routine EEG is often aided by more intensive evaluation, including extended electrocardiographic recording, tilt-table testing, screening of blood chemistry and hematology, and long term video-EEG monitoring. The portent of even a single seizure in an elderly patient with risk factors for epilepsy is great, carrying an 80% risk of recurrence.[302]

Once a diagnosis of epilepsy is established, treatment considerations and ongoing management are complicated by the physiologic changes that accompany aging. Antiseizure drug pharmacokinetics are altered as hepatic metabolism, protein binding, creatinine clearance, and overall blood flow decrease.[303,304] Serum levels for a given dose of phenytoin prescribed to elderly patients, for instance, vary widely both between patients and over time for a given patient.[305] For highly protein bound antiseizure drugs such as phenytoin and valproate, total serum levels may not accurately predict free drug levels in the setting of reduced albumen, and free drug levels should be assessed. Reduced renal clearance of drugs such as levetiracetam and gabapentin can also increase serum levels out of proportion to dose. In general, lower doses of antiseizure drugs are required to maintain therapeutic levels, and elderly patients are particularly susceptible to the adverse side effects of even therapeutic ranges of antiseizure drugs as the compensatory capacity of cognitive, sensorimotor, and proprioceptive systems diminishes.[306]

The incidence of adverse reactions to antiseizure drugs is high among elderly patients with epilepsy. With traditional agents, more than 50% experience short-term, long-term, and idiosyncratic adverse effects including impaired cognition, decreased bone mineral density, osteomalacia and osteoporosis, gait disturbance, falls and fractures, and occasionally urinary incontinence.[307] The significance of side effects is also amplified among the elderly, and the cognitive impairment and neurotoxicity associated with antiseizure drugs compound those related to concurrently prescribed medications.[308] Medication-related dizziness, tremor, ataxia, and encephalopathy can all occur at lower blood levels than in younger patients and place elderly patients at risk of falls, fractures, head injury, and wounds even when direct seizure-related injury is taken out of the equation.[309] Idiosyncratic reactions, affective changes, and cognitive dulling can disproportionately affect the psychosocial well being and overall functional level of patients already at risk for dwindling social networks and supports. Weight gain associated with drugs such as valproate, gabapentin, pregabalin, and carbamazepine can exacerbate type-2 diabetes.[310] Bone health is major concern for elderly patients, and the potential deleterious effects of some antiseizure medications on bone mineral density was previously discussed.

The impact of tolerability on drug effectiveness is reflected in the low retention rates of elderly subjects in prospective comparative trials of antiseizure drugs. In the VA Cooperative Study 428 comparing carbamazepine, gabapentin, and lamotrigine for newly diagnosed epilepsy in elderly patients (65 years and older), >50% had terminated the trial by 12 months, and approximately 40% of these were for adverse events.[86] Lack of seizure control was seldom a cause for dropout. Furthermore, there was a statistically significant difference between the compared drugs in terms of trial retention (gabapentin and lamotrigine outperforming carbamazepine) that was not explained by differences in efficacy.

Drug-drug interactions are a major concern in elderly patients, who often take numerous medications. In one study, elderly patients treated with antiseizure medications were taking on average more than five concomitant drugs.[308] Indeed, many of the drugs used to treat the very conditions associated with development of adult-onset epilepsy interact with antiseizure medications. A combination of warfarin and phenytoin, for instance, can have unpredictable effects on a patient's INR, as hepatic metabolism of warfarin is induced, potentially reducing its anticoagulant effect. Similarly, enzyme-inducing antiseizure drugs reduce serum levels of atorvastatin, lovastatin, simvastatin, and fluvastatin, frequently prescribed cholesterol lowering agents.[311] Donepezil, often prescribed for treatment of dementia and metabolized by the CYP3A4 hepatic isoenzyme, is cleared more quickly in patients taking carbamazepine, phenobarbital, or phenytoin. Propoxyphene, in addition to being a poor analgesic for elderly patients, inhibits CYP3A4, and can lead to toxicity of coadministered carbamazepine. Other major drug-antiseizure drug interactions are included in Tables 3–15 and 3–16, but recognition of the potential for interactions should prompt careful review of medication lists and cross referencing. In general, avoidance of antiseizure drugs that affect liver metabolism reduces the likelihood of adverse interactions with existing drugs or drugs that may be required in the future by this population of patients who often have multiple medical conditions requiring

treatment.

Despite these well-documented problems, drugs associated with a high burden of interactions and adverse side effects continue to be prescribed for elderly patients. In one U.S. survey, phenytoin, carbamazepine, and phenobarbital accounted for 59.6%, 16.6%, and 16.6%, respectively, of the antiseizure drugs prescribed for elderly patients with epilepsy in skilled nursing facilities.[312] In another review of prescribing practices in the United States, pharmacokinetically and pharmacodynamically problematic combinations of antiseizure drugs (e.g., concomitant phenytoin and phenobarbital) were prescribed to 72% of elderly nursing home residents.[313] These practices are likely influenced by familiarity with traditional drugs among the primary care clinicians who tend to be the principle providers of epilepsy care to elderly patients. Cost may also play a role. The utility of newer agents with more favorable side-effect profiles is offset by their higher direct cost, especially in a group for whom multiple medications for coexisting conditions comprise a considerable financial burden. However, long-term analysis of the expense of medical care for adverse events and seizure recurrence from medication nonadherence has not been rigorously investigated and some have argued may favor drugs that are immediately more costly but better tolerated.[314]

The evidence base for choosing an antiseizure drug for newly diagnosed epilepsy in older patients is sparse; elderly patients are routinely excluded from most phase IV trials of new drugs. As described previously, the VA Cooperative Study 428 comparing carbamazepine, gabapentin, and lamotrigine found these drugs equally efficacious, but carbamazepine was less well-tolerated.[86] An earlier double-blind comparison of lamotrigine and carbamazepine for partial-onset and tonic-clonic seizures in the elderly demonstrated better tolerability with lamotrigine.[315] Based largely on these results, a 2005 ILAE analysis concluded that there is class I or II evidence to support using carbamazepine, gabapentin, or lamotrigine for partial-onset seizures in elderly adults.[83] Open-label adjunctive trials of gabapentin and levetiracetam for patients with established epilepsy showed that these agents were at least as efficacious in their elderly cohorts.[316,317] Beyond these data, case series and experience inform the choices made by many clinicians treating epilepsy. Surveyed epilepsy experts preferred lamotrigine, gabapentin, carbamazepine, oxcarbazepine, and levetiracetam (in that order) for first-line treatment of partial-onset seizures in elderly patients.[318] Once efficacy for seizure and epilepsy type are weighed and pharmacokinetic interactions considered, the rationale for choosing an individual drug rests on individual patient characteristics and should be based on avoiding potential problems. In addition to problems discussed previously, specific clinical situations might warrant avoidance of certain drugs. Gabapentin and pregabalin occasionally cause weight gain and peripheral edema that can complicate other medical conditions. Valproate, beyond its potential for protein binding interactions with other drugs, can produce or exacerbate action tremor in a dose-dependent manner. Although sometimes better tolerated than carbamazepine, and with less potential for drug-drug interactions, oxcarbazepine increases the risk of hyponatremia. This effect is most likely the result of increased renal tubule sensitivity to antidiuretic hormone (ADH). Oxcarbazepine-induced hyponatremia is seen far more often in elderly patients than in younger adults or children, is compounded by sodium-depleting diuretics, and can reduce seizure thresholds.[319] Topiramate and zonisamide generally cause more negative neurocognitive effects than other newer antiseizure drugs, but can also facilitate weight loss, which might be advantageous depending on clinical circumstances.

Elderly people comprise a significant and growing population of patients with epilepsy, have a higher prevalence of epilepsy than younger adults, and are disproportionately affected by the negative effects of antiseizure drug treatment. On the positive side, late-onset epilepsy is generally easier to control with modest drug doses of an initial drug than partial epilepsy in younger patients.[226] Therapy decisions should focus on issues of pharmacokinetics, tolerability, concomitant medications, and coexisting medical problems.

Psychiatric Disorders

The prevalence of psychiatric disorders among people with epilepsy is approximately twice that of the general population.[320] The observation that psychiatric disorders are more prevalent in epilepsies with known underlying brain dysfunction (temporal lobe epilepsy) than idiopathic epilepsy (juvenile myoclonic epilepsy) raises the question of a common underlying neurologic substrate,[321] although the psychosocial impact of a debilitating and chronic condition is likely a strong contributing factor.[322] Regardless of causation, the intermingling of psychiatric and epileptic conditions presents a two-way challenge of treating either condition without causing deterioration of the other. A more positively framed but difficult to achieve goal is that of treating each condition in a way that enhances control of the other.

Antiseizure medications are psychotropic medications, and have CNS actions beyond dampening epileptic discharges, including effects on mood, thought, and behavior. A general rubric for predicting the psychotropic properties of antiseizure medications has been proposed that roughly distinguishes drugs that are sedating, GABAergic, antimanic, and anxiolytic from those that are activating, antiglutaminergic, antidepressant, and anxiogenic.[323] In practice, the mixed mechanisms of antiseizure drugs as well as their complex interaction with the disease process of epilepsy can muddy close correlation of a drug's major mechanism with its psychotropic effect. Additionally, most available literature on the psychotropic effects of antiseizure drugs regards their use in patients with psychiatric disorders and cannot be assumed applicable to patients with epilepsy. Table 3–20 provides a general outline of potential antiseizure drug effects on psychiatric disorders.

Table 3–20 Antiseizure Drugs in Psychiatric Illness

	Antiseizure Drugs	
Psychiatric Condition	**Possibly Positive Effects**	**Possibly Negative Effects**
Depression	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine	Barbiturates Benzodiazepines Levetiracetam Topiramate Tiagabine
Anxiety	Benzodiazepines Gabapentin Pregabalin Tiagabine Valproate	Felbamate Lamotrigine Levetiracetam
Bipolar disorder	Carbamazepine Gabapentin Valproate	
Psychosis		Ethosuximide Topiramate Zonisamide





Depression

Depression occurs in ~30% of patients with epilepsy.[324] Barbiturates have long been associated with development or exacerbation of depression, particularly so among

children, and stand out as the class of antiseizure drugs most likely to cause affective deterioration.[325,326] Carbamazepine and valproate have been associated with mood-elevating effects, and phenytoin with an equivocal mixture of prodepressant and antidepressant effects.[327] Valproate continues to be a standard treatment for bipolar disorder. Also used for bipolar disorder and with a moderate anxiolytic effect, gabapentin has shown a mood-elevating effect in some patients with epilepsy.[328] Lamotrigine has shown good effect against bipolar I (depressed phase) and rapid cycling bipolar disease.[329,330] Caution is advised when interpreting these data, which may not necessarily transfer from patients with primarily psychiatric disease to patients with epilepsy.

Several antiseizure medications have the potential to worsen or result in de novo affective dysfunction. The underrecognized provocation of nonconvulsive status epilepticus with tiagabine likely confounded accurate reporting of behavioral or affective changes during early clinical trials, but the incidence of both depressed mood and nervousness exceeded that of placebo in later add-on trials.[331] Information regarding topiramate is mixed. While it appears to have some benefit in patients with bipolar disorder who have failed other medications, topiramate has a dose-dependent association with development of depression in patients with epilepsy.[332–334] Levetiracetam does not show a clear risk of depression, but can cause agitation and irritability that is sometimes associated with preexisting dysphoria.[335,336]

Anxiety

Anxiety disorders occur in ~10%–20% of patients with epilepsy, but the interplay between these conditions is complex.[324] Anxiety can be a direct ictal symptom when seizures affect the limbic system, a postictal occurrence of dysphoria, or a more lingering interictal phenomenon. Seizure worry and depression are two of the most important factors associated with quality of life in patients with medically refractory epilepsy.[6] Benzodiazepines, well-established in the short-term treatment of anxiety, have clear efficacy against seizures but their use is limited by sedative side effects and development of tolerance. Gabapentin, pregabalin, tiagabine, and valproate have all shown beneficial effects in trials for the treatment of anxiety disorders.[337–340] Whether antiseizure drugs can worsen anxiety or provoke a new anxiety disorder is less clear. Felbamate, which activates alertness and can cause insomnia and agitation, appears to exacerbate anxiety in patients predisposed by prior anxiety disorders.[341] While drugs such as lamotrigine and levetiracetam have not been specifically linked to development of anxiety, when patients are switched to these from more sedating and cognitively dulling drugs a behavioral release effect may occur and preexisting symptomatology may emerge.[342] Topiramate has been associated with a higher rate of mood lability than placebo in add-on trials.[343]

Psychosis

Psychosis occurs in ~2%–7% of patients with epilepsy.[324] Psychotic symptoms in epilepsy are classified by their temporal relationship to seizures, either ictal, postictal, or interictal. Interictal psychoses often raise the longstanding and thorny issue of whether patients experience an antagonistic relationship between epileptic and psychiatric symptoms—so-called forced normalization of the EEG during which psychosis occurs followed by periods of increased convulsive activity.[344] More commonly, psychosis coexists with epilepsy in a more chronic interictal form. There are no antiseizure drugs that have been demonstrated effective against schizophrenia. Conversely, several antiseizure drugs have the potential to cause psychosis. Ethosuximide has been linked to psychosis in children and adults and has classically been described in association with the forced normalization phenomenon.[345] Topiramate and zonisamide have also been linked with psychosis, the latter likely in a dose-dependent fashion.[346]

Psychotropic drug exacerbation of epilepsy

Patients with coexisting epilepsy and psychiatric disorders should be provided adequate treatment with psychotropic drugs where indicated without compromising seizure control. Psychotropic drugs interact with antiseizure medications as highlighted previously, but also can have an effect on epilepsy itself. A number of psychotropic drugs have proconvulsant effects. Recognizing which do and to what degree guides their use in patients with epilepsy.

Antipsychotic drugs can lower seizure threshold in patients with epilepsy, but there is a paucity of evidence for validly stratifying this effect beyond generalities. Phenothiazines likely cause the highest risk of seizures in a dose-related fashion, against which other antipsychotics are compared. Chlorpromazine has been associated with a 0.5% risk of seizures at doses <1000 mg that rises to 9.0% at doses >1000 mg.[347] Clozapine's risk is similarly dose-related, 1.0% at <300 mg and 4.4% at ≥600 mg.[348] Clozapine also compounds the risk of agranulocytosis associated with some antiseizure drugs. Of the newer compounds, both olanzapine and risperidone are associated with a low risk of seizures and are often recommended for patients with epilepsy.[349] Between these there are a range of antipsychotics for which accurate risk of seizure provocation is unclear. Overall, with noted exceptions, the risk of seizure exacerbation does not warrant avoiding antipsychotic drugs as a class if necessary for psychiatric stability.

Most antidepressants carry warnings about the risk of causing seizures. The most commonly prescribed antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), carry a uniformly low risk of seizures (most <0.1%) and in general are safe to use in patients with epilepsy.[350] With the exception of clomiprimine, which carries a risk of 0.7%–3.0%, tricyclics are also relatively safe. Bupropion has a dose-dependent and formulation-dependent association with seizures. Doses <450 mg/day confer a 0.6%–1.0% risk of seizures, but above 450 mg, the risk of seizures increases to 0.6%–2.19%.[350] The sustained release formulation of bupropion at doses of 300–400 mg/day has the lowest risk of seizures, 0.1%–0.4%. With a high incidence and association with diminished quality of life in epilepsy, depression warrants aggressive treatment. As with psychosis, the potential benefit of pharmacotherapy far outweighs the minimal risk of seizure threshold reduction provided appropriate drug choices.

Intellectual and Developmental Disabilities

Patients with IDDs present unique diagnostic and therapeutic challenges to the treatment of epilepsy. Yet the principles of treatment that govern therapeutics in the general epilepsy population hold true for those with IDD—maximizing seizure control with appropriately chosen medications; minimizing side effects, and in particular the potential additive side effects of polypharmacy; and promoting optimal quality of life. As a group, patients with IDD have a higher rate of epilepsy than the general population, higher rates of symptomatic partial or symptomatic generalized epilepsies, and as a result, higher rates of medically intractable epilepsy.[243,244,351] These trends, in concert with the challenges that accompany evaluating epilepsy and monitoring treatment in a patient with intellectual impairments, can engender pessimism as well as ill-founded tolerance of adverse treatment effects.

When designing an antiseizure drug regimen for patients with IDD it is important to recognize that the level of intellectual and physical disability and severity of EEG abnormalities correlate poorly with the likelihood of seizure control. Rather, as is the case in the general epilepsy population, the type of seizures and number of seizure types are the primary predictors.[352,353] Polypharmacy is a significant concern among patients with IDD, many of whom have had layer upon layer of antiseizure drugs added in an attempt to control difficult-to-control seizures. Far from being immune to the additive neurotoxic effects of antiseizure medications, patients with IDD actually may have a lower compensatory neurologic reserve that renders them more and not less susceptible to sedating, cognitively dulling and adverse behavioral side effects of antiseizure medications.[354] Several studies have directly addressed the potential benefits of simplifying antiseizure regimens in this population, demonstrating that seizure control is rarely compromised and often improved with additional enhancement of behavior and alertness when drug regimens are simplified. In one trial, monotherapy was achieved in 77% of a pediatric cohort with IDD noting improvement in alertness, responsiveness, and educational performance without loss of seizure control.[355] In another trial conversion to valproate monotherapy or combination of valproate with one other drug resulted in seizure freedom among approximately half of subjects with IDD and >50% seizure reduction in the other half.[356] And in a long term prospective trial, 58% of patients with IDD converted to monotherapy experienced no worsening of seizures, and 50% of those who had been seizure free experienced no further seizures over the subsequent 10 years.[357] Monotherapy is thus an attainable goal provided the doses required to control seizures do not result in unacceptable side effects.

Choosing among available drugs for an appropriate regimen is not informed by well-designed clinical comparison trials for patients with IDD and epilepsy, and patients with IDD are not a homogeneous population. Instead, choice of medication should remain guided by the efficacy of drugs for identifiable seizure types and syndromes, as well as avoidance of short-term and long-term side effects. The safety and tolerability profiles of antiseizure medications such as phenobarbital and phenytoin make them less than optimal therapies for patients with IDD, and as a group, newer antiseizure medications appear well tolerated and effective.[358–362] Many patients with IDD have complicated

mixtures of focal onset and symptomatic/cryptogenic generalized seizures and broad spectrum agents are often required. As enumerated previously, drug regimens appropriate for treatment of Lennox-Gastaut syndrome and that are unlikely to exacerbate seizures may often be beneficial for patients with IDD, including lamotrigine, levetiracetam, topiramate, and zonisamide.[141,363,364] Felbamate, usually avoided due to association with life-threatening aplastic anemia and liver failure, should be considered for patients with IDD whose tonic or atonic seizures place them at risk of serious injury outweighing this drug's potential drawbacks.[136] Repetitive or prolonged seizures may occur, and appropriate prophylaxis should be coupled with a plan for rescue treatment. Rectal diazepam is safe and effective when administered according to a well defined plan that includes clear criteria of seizure length or pattern of repetition.

Insertion of a VNS can be a helpful adjunctive nonpharmacologic treatment in patients with such injurious seizures, potentially reducing the frequency and severity of clustered or prolonged seizures. Corpus callosotomy, partial severing of the interhemispheric connections that mediate tonic and atonic seizures, is rarely performed due to morbidity intrinsic to the procedure, but in some case should be considered when other treatments fail.

Evaluation of antiseizure drug side effects requires a high level of suspicion and careful attention to changes in behavior or demeanor. For lack of an accurate way to articulate the adverse effects of drugs, patients with IDD may demonstrate only general or subtle changes in behavior that indicate trouble with their treatment. For instance, dizziness and ataxia may manifest as reluctance to ambulate or participate in usual activities. Depressive symptoms may show up as a diminished interest in social activities, aggression, or irritability. Indeed, any appreciable change in physical, social, academic, or occupational function, problems with performing activities of daily life, or alterations in mood in the context of a new or adjusted antiseizure medication should prompt consideration of drug-related side effects. Potential chronic effects of antiseizure medications should be deliberated when choosing treatment. Patients with IDD are predisposed to osteoporosis due to diminished weight-bearing activity, lack of sun exposure, and possibly inadequate calcium intake, and the accelerated bone loss associated with hepatic enzyme-inducing drugs compounds this problem.[365] Weight gain is also a problem in patients with limited physical activity and can have deleterious long term health effects.

The apparent emergence of worsened seizures or new seizure types in patients with IDD should prompt a healthy measure of clinical skepticism before launching a change in or addition to drug regimens. The seizures experienced by patients with IDD often stretch the boundaries of semiological categories, but for individual patients new seizure types are rare. Abnormal neurological function at baseline raises the potential that changes in behavior will be mistaken for epileptic events. In a study of 63 patients with IDD evaluated by video-EEG monitoring for the appearance of new seizure types, ~40% of behavioral events believed to be seizures were not.[366] Instead, medication side effects accounted for a considerable proportion of suspected seizures. Others, who exhibited agitation or difficult behaviors attributed to seizures from medication withdrawal were in fact being themselves without the obtunding mantle of sedative drugs.

Treating epilepsy in patients with IDD is challenging. The underlying principles of treatment, however, match those applicable for any patient with epilepsy and instead of producing pessimism, foster hope that if properly applied, seizure control and quality of life can be improved.

Status Epilepticus

Status epilepticus (SE) is a neurologic emergency with a 30-day mortality that approaches 22%, depending on the duration of SE before treatment, the underlying etiology, and the patient's age.[367] Historically, SE has been defined as >30 minutes of either continuous or repeated seizures without full recovery of consciousness.[368] However, in recognition of the clear relationship of treatment efficacy to early initiation and the higher morbidity of seizures allowed to persist, a more stringent definition has been proposed: seizures continuing for more than five minutes or repeated seizures within that time with incomplete recovery.[369] While the latter criteria have not been completely accepted in practice or in studies of treatment for SE, many clinicians endorse them as an operational definition that stresses the exigency of early recognition and treatment of SE.

Status epilepticus can be classified into generalized convulsive status epilepticus (GCSE) and nonconvulsive status epilepticus (NCSE). Generalized convulsive SE is the more clinically apparent of the two, manifesting as ongoing tonic or clonic activity ofthe extremities, but may evolve over time into more subtle findings of eye deviation, nystagmus, or subtle facial, eyelid, or finger twitching.[370] Nonconvulsive SE consists of continuous generalized electrical seizure activity without overt convulsions, and is thus an EEG entity often accompanied by signs of agitation, delirium, nystagmoid eye movements, or automatisms. Nonconvulsive SE is further divided into absence or partial NCSE depending on EEG criteria. Absence SE is a relatively benign form of NCSE, while complex partial NCSE is associated with a significant degree of neuronal injury, morbidity, and mortality.[371]

Early termination of seizures without increasing morbidity is the benchmark of successful SE treatment. As a rule, SE becomes more difficult to treat the longer it persists. Cellular internalization of GABA receptors and enhancement of glutaminergic transmission may contribute to the development of pharmacoresistant SE over time.[38] Treatment approaches and algorithms can be divided into prehospital, hospital, and intensive care settings.

Status epilepticus often begins outside of hospitals, and treatment should not be delayed until arrival at an emergency department. Use of benzodiazepines by first responders has been shown superior to placebo in efficacy for terminating SE and reducing complication rates prior to arrival at a hospital, with lorazepam more effective than diazepam (59.1% versus 42.6%).[372] Use of lorazepam 2–4 mg or diazepam 5–10 mg is appropriate. When IV access cannot be obtained, intramuscular or rectal administration of benzodiazepines is possible.

Once in hospital, and in addition to basic life support, airway maintenance, IV fluid resuscitation, cardiac monitoring, and workup with treatment of the underlying cause of SE, EEG monitoring should be commenced as soon as possible; paralytic agents often employed to secure respiratory function can mask the clinical evidence of ongoing seizures. None of these measures, however, should delay the rapid initiation or continuation of pharmacologic treatment for SE. The goals oftreatment are prompt cessation of seizures, prevention of recurrence, and minimization of adverse treatment effects. These goals underlie the following algorithm.

Initial treatment in hospital should be immediately commenced with lorazepam 0.1 mg/ kg infused at 2 mg/min. Historically, lorazepam and diazepam have been considered interchangeable, but pharmacokinetic and clinical evidence support the superiority of lorazepam. Diazepam is highly lipid soluble and enters the CNS more rapidly than lorazepam, but also rapidly redistributes to peripheral fat stores, curtailing the duration of its effect.[373] In practice, lorazepam has an onset of clinical antiseizure effect similar to that of diazepam, but a longer duration of effect (12 hours versus 20–30 minutes). Sustention of effect is important, and breakthrough seizures after initial cessation have been seen in approximately 50% of patients treated for convulsive SE with intravenous diazepam.[374] A meta-analysis of randomized controlled trials comparing several anticonvulsants to each other and to placebo affirms the consensus of standard clinical practice that lorazepam is more effective than diazepam or phenytoin in rapidity of action, maintenance of efficacy, and incidence of adverse events.[375] Treatment with benzodiazepines alone may be sufficient in a significant proportion of patients, particularly when a recognized underlying etiology can be rapidly ascertained and corrected.[376] Incomplete cessation of seizures 5–7 minutes after completing a benzodiazepine infusion warrants use of a second agent

The most commonly recommended second (but still first-line) treatment for SE is either intravenous phenytoin or fosphenytoin at a loading dose of 20 mg/kg. The frequently encountered approach of administering a gram of phenytoin is insufficient for most adult patients.[377] An additional 10 mg/kg can be given if seizures persist. Due to infusion rate-dependent cardiovascular effects (hypotension, QT prolongation, dysrhythmia) phenytoin should be administered at a maximal rate of 50 mg/min. By contrast, fosphenytoin can be infused at 150 mg/min. Fosphenytoin's putatively better safety profile is theoretically explained by its solubility in water. Phenytoin, poorly water soluble, requires a noxious propylene glycol diluent for IV preparation. In practice, the incidence of cardiovascular adverse events is similar for both agents.[378] The difference in rapidity of administration is significant. For a 70 kg adult, a safely infused 20 mg/kg loading dose of phenytoin should take approximately 30 minutes. A full loading dose of fosphenytoin, on the other hand, can be infused in as little as 10 minutes. In the setting of SE, where speed of treatment is paramount, fosphenytoin's rapid infusion rate gives it a conceptual efficacy advantage over phenytoin, but this has not proven the case either clinically or in measurements of time to peak phenytoin concentration. The speed of fosphenytoin's administration is offset by the time required for its metabolism by tissue phosphatases from prodrug to active phenytoin, with a conversion half-life of 8–15 minutes. As a result, intravenous phenytoin and fosphenytoin both produce free serum phenytoin concentrations of ~1 mg/mL within 10 minutes of infusion commencement.[379] Fewer infusion site complications are experienced with fosphenytoin than with phenytoin. Extravasation of phenytoin with severe reaction of tissue adjacent to the infusion site, the purple glove syndrome, was reported to occur in ~6% of exposed patients in one series.[380] More moderate infusion site discomfort and irritation also occur more commonly

with phenytoin than with fosphenytoin.[381]

If seizures persist despite treatment with benzodiazepines and phenytoin or fosphenytoin, SE is considered refractory to treatment. Therapy for refractory status epilepticus (RSE) follows one of two general pathways, both of which require endotracheal intubation, possibly vasopressor support, and an ICU level of care. Traditionally, intravenous phenobarbital has been the next step after phenytoin/fosphenytoin, administered at 20 mg/kg at a rate of 50–75 mg/min. Of neurologists surveyed in 2001, 45% preferred nonanesthetic doses of IV phenobarbital for second-line treatment upon failure of first-line agents, and 15% chose IV valproate.[382] But a significant number advocated progression of treatment to continuous anesthetic dose anticonvulsant infusions, choosing either midazolam, pentobarbital, or propofol. The U.S. results roughly matched those of a similar European survey in 20 03.[383] A clear practice consensus of how best to approach RSE has not yet been established.

Second-line anesthetic anticonvulsants are given as loading doses followed by continuous infusions. Clinical status is difficult to ascertain under anesthesia, and level of treatment is normally followed with continuous EEG monitoring. Titration of treatment to a suppression-burst pattern on the EEG remains standard, but the recommended degree and length of suppression-burst maintenance lacks evidence or consensus. Most clinicians continue second-line continuous IV treatment titrated to EEG suppression-burst for 48 hours before lowering or withdrawing anesthesia to assess for clinical and EEG improvement. Intravenous pentobarbital, a short-acting barbiturate, is effective for RSE but associated with myocardial depression, hypotension, and immunosuppression that complicates is use in critically ill patients.[377] Midazolam is a short-acting benzodiazepine advantageous for the fast recovery of consciousness that can be accomplished upon its discontinuation. Although less likely to produce hypotension than either propofol or pentobarbital, tachyphylaxis can develop requiring escalating doses.[384] Propofol is a GABA-A receptor agonist similar in action to benzodiazepines and barbiturates and has rapid onset and offset of action. Propofol is avoided in children due to the potential for a bradyarrhythmias, hyperlipidemia, enlarged fatty liver, and severe metabolic acidosis, the propofol infusion syndrome.[385] Collection of various reports of higher mortality associated with use of propofol in adults has raised questions about its overall safety.[386] A meta-analysis comparing advantages and disadvantages of midazolam, pentobarbital, and propofol suggested pentobarbital superior to midazolam and propofol in efficacy, but associated with a higher occurrence of hypotension requiring pressor support. There was no overall difference in mortality among the three.[387]

The morbidity and mortality of RSE is high regardless of which therapeutic pathway is taken, a dynamic that is likely attributable to the gravity of the medical problems that underlie seizures that don't respond to initial treatment.[388–389] In addition to the severity of etiology, delayed or suboptimal initial treatment also contributes to development of RSE.[390] The vital components of appropriate treatment for SE remain early recognition and early, aggressive, informed pharmacotherapy.

CONCLUSION

Epilepsy is a syndrome characterized by an enduring predisposition to seizures and it encompasses many conditions. The accurate identification of these guides appropriate treatment choices from an array of available therapies. In the past two decades, the range of drugs for prevention of seizures in people with epilepsy has expanded considerably, as has our understanding of how they work. With variety comes complexity, and applicability to seizure and epilepsy type, safety, and tolerability profiles, pharmacokinetics, effects on comorbidities, and suitability for individual patient characteristics must all be carefully considered when providing and monitoring drug therapy in epilepsy. A tripartite goal underlies each of these considerations: no seizures, no adverse side effects, and optimal quality of life.

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Migraine

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Headache may be the most common of all human ailments. It is also the most common complaint of patients evaluated by neurologists. A large percentage of headache patients will be diagnosed as having migraine, a specific subtype of headache afflicting approximately 10%—20% of the population.[1] At present, the diagnosis of migraine rests solely on clinical criteria.

Migraine is a specific neurological syndrome that has a wide variety of manifestations. At the most basic level, migraine without aura can be defined as a throbbing (usually unilateral) headache with associated nausea. A prodromal phase may last as long as 24 hours before the headache and may consist of mood and appetite changes. Migraine with aura is usually preceded or accompanied by a focal neurological event. The aura is most commonly experienced as a visual alteration but may involve sensory and/or motor changes. Auras may also occur without an associated headache. The headache itself is often accompanied by photophobia, hyperacusis, polyuria, and/or diarrhea. A migraine attack usually lasts from hours to days and is followed by prolonged pain-free intervals. The headache frequency is extremely variable but usually ranges from 1–2 per year to 1–4 per month. The International Headache Society (IHS) has developed specific detailed criteria for the diagnosis of migraine and other types of headaches.[2]

The morbidity associated with the millions of migraine sufferers is staggering. It is estimated that approximately 112 million workdays are lost each year in the United States due to migraine.[3] However, drugs that are effective in the acute and prophylactic treatment of migraine are readily available so it is imperative that physicians initiate appropriate treatment for migraine.

This chapter is intended to provide a review of the current state of knowledge concerning the biological basis and treatment of migraine.

Pathogenesis of migraine

"The cause of migraine remains unknown" is a generally accepted statement today despite the fact that a significant and varied literature exists that suggests a specific biological basis of migraine. Indeed, it is now unequivocal that migraine susceptibility results from a combination of physiological stressors and underlying genetic variables.

Physiological Stress and Migraine

The fact that monozygotic twins with migraine are only concordant in 20%–50% of cases indicates that environmental factors play a major role in the pathogenesis of migraine.[4] Indeed, a large number of environmental stimuli that result in physiological stress are known to induce a migraine attack.[5] These trigger factors all represent a change, often sudden, in the internal or external environment. Common migraine trigger factors include:

- mental and/or physical stress (and sudden relief from stress)
- missing a meal
- hypoglycemia
- dietary triggers (e.g., red wine, cheeses)
- hormonal fluctuations
- altitude changes
- weather changes



- ethanol
- sleep disturbances
- olfactory stimuli
- bright sunshine
- exercise

These trigger factors are cumulative. Although a single trigger factor can induce a migraine attack, it is much more common to be able to identify multiple, concurrent trigger factors for any single attack.

Genetic Basis of Migraine

Migraine susceptibility has a definite genetic component. Technological advances in the field of molecular genetics have been applied successfully to the analysis of migraine since the 1990s.[6,7] Specific mutations leading to rare causes of vascular headache have been identified (Table 4–1), although genetic variations that modulate the susceptibility to the more common forms of migraine have proved more difficult to establish. For example, Mitochondrial Encephalopathy, Lactic Acidosis, and Strokelike episodes (MELAS) Syndrome is caused by an A to G point mutation in the mitochondrial gene encoding for $tRNA^{Leu(UUR)}$ at nucleotide position 3243.[8] Episodic migraine-like headaches are another common clinical feature of this syndrome, especially early in the course of the disease. The genetic pattern of mitochondrial disorders is quite unique since only mothers transmit mitochondrial DNA. Thus, all of the children of mothers with MELAS will be affected with the disorder.

Table 4–1 Status of Migraine Genetics (as of 2007)

Gene (locus)	Function of Gene	Clinical Syndrome	Comment
tRNALeu(UUR) (Mitochondrial)	Unknown	MELAS Syndrome	Extremely rare syndrome
CACNL1A4 (19p13)	P/Q calcium channel regulating neurotransmitter release	Familial Hemiplegic Migraine 1 (FHM1)	Mutations account for approximately 50% of FHM cases
ATP1A2 (1q21-q23)	alpha-2 isoform of sodium-potassium-ATPase	Familial Hemiplegic Migraine 2 (FHM2)	Mutations account for sporadic FHM cases
SCN1A (2q24)	Sodium channel, brain type I, alpha subunit	Familial Hemiplegic Migraine 3 (FHM3)	Mutations account for sporadic FHM cases

Familial hemiplegic migraine (FHM) is characterized by episodes of recurrent hemiparesis or hemiplegia during the aura phase of a migraine headache. Other associated symptoms may include hemianesthesia or paresthesia, hemianopic visual field disturbances, dysphasia, and variable degrees of drowsiness, confusion, and/or coma. In severe attacks, these symptoms can be quite prolonged for days or weeks, but characteristically last for only 30–60 minutes and are followed by a unilateral throbbing headache.

Approximately 50% of cases of FHM appear to be caused by mutations within in the CACNL1A4 gene on chromosome 19.[9] Multiple distinct point mutations have now been identified within the gene (in different families) that cosegregate with the clinical diagnosis of FHM. An analysis of haplotypes in two independent families with the same mutation suggested that each mutation arose independently, rather than representing a founder effect. The function of the CACNL1A4 gene remains unknown but it is likely to play a role in calcium-induced neurotransmitter release and/or contraction of smooth muscle. Different mutations within this gene are the cause of another neurogenetic disorder, episodic ataxia type 2.

A second subtype of FHM, designated FHM2, is caused by mutation in the gene encoding the alpha-2 subunit of the sodium/ potassium pump (i.e., ATP1A2). In an Italian family with autosomal dominant FHM spanning 6 generations, a point mutation in the ATP1A2 gene was identified.[10] Different point mutations in the ATP1A2 gene have been identified in additional unrelated families with FHM.[11] DeFusco and colleagues[10] suggested that the mutations may lead to a functional increase in extracellular potassium, producing a wide cortical depolarization and an increase in intracellular potassium, which may promote an increase in intracellular calcium through the sodium/calcium exchanger. Thus, an increase in intracellular calcium might be similar to the physiological effect of CACNA1A mutations in FHM12.[10,11]

A third subtype of FHM, designated FHM3, is caused by mutations in the SCN1A gene, a voltage-gated ion channel essential for the generation and propagation of action potentials, primarily in neuronal and muscle cells.[12] The mutations linked to FHM have been identified in three unrelated families. Mutations in this gene also result in generalized epilepsy with febrile seizures.

In a 10-year-old boy with episodic ataxia, seizures, migraine, and alternating hemiplegia, a de novo mutation in the SLC1A3 (glutamate transporter) gene was identified.[13] The child had experienced four discrete episodes of ataxia and slurred speech, seemingly triggered by a febrile illness and at age six, he developed a severe right-sided headache followed by hemiparesis and decreased consciousness lasting five days. Magnetic resonance imaging (MRI) showed cerebellar atrophy. Thus, the individual has a variety of symptoms that are consistent with a diagnosis of FHM. Jen and colleagues[13] postulated a role for abnormal glutamate transmission in the neurological features seen in this patient. Future studies are needed to determine if this gene is involved in other subtypes of migraine.

The genetic basis of the more common forms of migraine have proved much more difficult to identify despite that fact that multiple epidemiological, twin, and familial studies have demonstrated a definite genetic component in the more common forms of migraine. Indeed, a number of genetic association studies have suggested a link between other genetic variants and the more common causes of migraine.[6,7] However, unlike with MELAS and FHM, these allelic variations are neither necessary nor sufficient to cause migraine. For example, a *NcoI* polymorphism in the gene encoding the D2 dopamine receptor (DRD2) was evaluated in a group of 250 unrelated individuals.[14] The study concluded that susceptibility to migraine with aura is modified by certain DRD2 alleles. Multiple other genes have been implicated in migraine based on reports of positive association studies (e.g., glutathione-S-transferase, dopamine type 4 receptor, tumor necrosis factor-β/lymphotoxin-α, serotonin transporter, the C677T methyl-tetrahydrofolate reductase allele, the dopamine-β-hydroxylase gene, and the angiotensin-converting enzyme allele).[6,7] However, none of these genetic associations studies has been replicated consistently. Therefore, these studies suggest that multiple genetic variations may significantly, yet subtly, alter susceptibility to the more common forms of migraine. Overall, the results of more than a decade of molecular genetic analysis indicate that migraine is a multifactoral genetic disorder with a strong environmental component.

Theories of migraine pathophysiology

A unifying biological hypothesis that can explain the pathophysiological basis of the migraine syndrome has been historically lacking. For example, Graham's statement that migraine "is an inherited disorder occurring in people who have both an undue tendency to seek stress and at the same time a deficiency in their physiological adaptation to stress" is true but the biological basis for this observation has remained elusive.[15] Although the pathophysiological basis of migraine remains unknown, several theories have been proposed to explain this common medical problem.

Vascular Theory of Wolff

Although various theories of migraine pathogenesis have been proposed for centuries, Harold G. Wolff is credited with developing the first scientifically derived hypothesis of migraine.[16] Based on the theories of Wolff that were developed in the 1940s and 1950s, migraine was considered to be a vasospastic disorder. Wolff and colleagues hypothesized that migraine results primarily from a series of vascular disturbances.

Interictal Period. The caliber of the temporal artery was observed to be significantly larger in migraineurs during headache free periods.[17] Interictal pain thresholds were normal, indeed, pain thresholds were not significantly lowered as late as one hour before an attack.[18]

Early Headache Phase. Vascular contractile variability was noted to increase in migraineurs as long as 72 hours prior to a migraine attack.[18] During the 24 hours prior to a headache, vasoconstriction was the predominate vascular state and was noted to be “frequently maximal during the minutes preceding the onset of the headache.”[18] This local vasoconstriction, as evidenced by a diminished pulse wave amplitude, and increased resistance to blood flow were observed frequently in temporal arteries and conjunctival vessels at the beginning of a migraine attack.[19] Wolff and colleagues noted that these changes “sometimes” occurred in association with visual auras but were “commonly unrelated.”[19] Subsequent interpretations of Wolff ’s data have often failed to note this important observation.

Late Headache Phase. A progressive vasodilatation, hyperemia, and diminished resistance to blood flow were observed in extracranial vessels. In more severe headaches, in the already dilated vessels, a relative inadequacy of vessel drainage was observed that led to an increased resistance to blood flow. Indeed, the blood flow rate on the affected side was estimated to be reduced as much as 5-fold during the peak of the headache phase.[18]

Moreover, the extracranial arteries were tender on palpation.[18] A progressively lowered threshold for deep pain over the frontal area supplied by the supraorbital artery was demonstrated on the side of the headache during an acute attack as the headache continued and worsened.[18] Initially, the region of lowered pain thresholds was circumscribed but it expanded (i.e., a secondary hyperalgesia) as the headache progressed. In addition, Wolff and colleagues noted that the increased pain sensitivity commonly outlasted the headache by hours or even days.

These detailed clinical observations continue to be of significant theoretical importance since it is well accepted that vasodilatation per se is not painful. Wolff and colleagues hypothesized that the accumulation of pain-producing or pain-threshold lowering substances within the dilated and mechanically tense perivascular space was the direct cause of the headache pain.[19,20] Whether these pain-producing substances derived from nerves and/or vascular sources was not determined.

At present, Wolff ’s hypothesis of an initial vasospasm of cranial blood vessels followed by a painful vasodilatation is often rejected because it is widely believed that the hypothesis is not able to explain all of the clinical features of the disorder. Specifically, the ability of the observed vascular changes to induce all of the symptoms of migraine has been questioned. For example, the decrease in blood flow that is observed during the vasoconstriction phase does not appear to be significant enough to cause focal neurological symptoms (although such symptoms are relatively uncommon). Moreover, vasodilatation alone cannot account for the lowered pain thresholds observed in migraineurs (although Wolff and colleagues were well aware of this fact). In addition, the nausea, vomiting, gastrointestinal changes, and other clinical features of a migraine attack seem to be unrelated to cranial vessel changes. Thus, it is unlikely that simple vasoconstriction and vasodilatation are the primary pathophysiological abnormalities in migraine, as was noted by Wolff and colleagues.[19]

Nonetheless, it is clear that significant vascular and pain threshold changes occur during a migraine attack. Therefore, the major observations made by Wolff and colleagues remain valid and must be explained by any unifying theory of migraine.

Cortical Spreading Depression (i.e., Spreading Depression of Leao)

The work of Olesen and colleagues has led to the suggestion that migraine results from spreading depression of cortical electrical activity (i.e., spreading depression of Leao).[21] Spreading depression is an electrical phenomenon observed in nonhuman species that occurs in the cerebral cortex in response to noxious stimuli. A focal reduction in electrical activity and increase in blood flow occurs and then spreads across the hemisphere at the rate of 2–3 mm per minute.[22] The electroencephalogram (EEG) of the animal returns to normal within approximately 10 minutes but evoked cortical responses may be depressed for as long as an hour after the noxious stimulation. Cerebral blood flow during and after spreading depression in rats has been studied by autoradiographic methods.[23] These studies demonstrated that cortical blood flow is reduced by 20%–25% following induced spreading depression.

Olesen and colleagues[24,25] studied regional blood flow changes in patients during a classical migraine attack. A gradual spread of reduced blood flow was observed starting in the occipital region and advancing anteriorly. Importantly, these blood flow changes did not correspond to the distribution of the major intracranial arteries. However, the observed flow changes were similar to the electrical phenomenon of spreading depression of Leao. Olesen and colleagues[25] speculated that the aura of classic migraine might occur secondary to the spreading oligemia observed in classic migraine patients. This theory states that migraine results from an evolving process in the cerebral cortex that occurs secondary to decreased cortical function, decreased cortical metabolism, and/or vasoconstriction of cortical arterioles.[21]

However, regional oligemia has not been observed in common migraine patients. Lauritzen and Olesen[26] studied 12 patients within 20 hours of the onset of a common migraine. There were no changes in focal or global cerebral blood flow in any of the patients. In addition, Olesen and colleagues[25] studied 12 patients in whom attacks could be provoked by red wine. In studies of patients in which migraine could be induced, regional cerebral blood flow studies were all within normal limits. Thus, regional cerebral blood flow seems to be normal during a common migraine attack in contrast to the changes that have been reported in a classic migraine attack. While the theory of spreading depression is quite interesting, it must be noted that this electrical phenomenon has never been recorded in humans during a migraine attack.

The Trigeminovascular System in Migraine

In 1910, Bruce observed that the application of mustard oil to the conjunctival sac in experimental animal models produced inflammation that could be blocked by sensory nerve ablation.[27,28] These early studies of the sensory neuron-induced “wheal and flare” reaction led to the concept of neurogenic inflammation (NI), referring to both vasodilatation and increased vascular permeability arising from the retrograde release of neuropeptides by capsaicin-sensitive sensory neurons in the periphery.[29] Neurogenic inflammation was thus recognized as a physiological process of inflammation induced by the nervous system.

The modulation of both local blood flow and vascular permeability by small-fiber sensory neurons (C fibers and some Aδ fibers) is now well-established. At the molecular level, this modulation is mediated by the peripheral release of neuropeptides such as substance P (SP), neurokinin A (NKA), endothelin-3 (ET-3), and calcitonin-gene related peptide (CGRP). Direct chemical, thermal, or electrical stimulation of sensory nerves in rodents induces vascular permeability changes that are mediated predominantly by the tachykinins (e.g., SP and NKA) and vasodilatation (i.e., the axon reflex flare) that is mediated predominantly by CGRP.[30]

A possible relationship between NI and migraine was first suggested by Dalessio,[31,32] who stated that migraine occurs as a result of vasodilatation associated with a sterile local inflammatory reaction. In 1984, Moskowitz extended this relationship when he proposed a mechanism for migraine headaches that involves depolarization-induced release of SP or other neuropeptides from trigeminal terminals; these neuropeptides were postulated to increase vascular permeability and dilate cerebral blood vessels.[33] The NI theory of migraine was advanced considerably by the development of rodent models of NI that allowed for the detection of plasma protein extravasation (PPE) in the dura following chemical, electrical, or immunological stimulation.[34–43] Vascular permeability changes consistent with inflammation (i.e., PPE) and induced by SP released from trigeminal neurons was posited to play a key role in migraine pathophysiology with either a limited, or no role for neurogenic vasodilatation (NV) induced by CGRP.[44]

Despite the continued widespread acceptance of NI as an essential component of the pathophysiology of migraine,[45–51] a definitive role for dural NI in the pathophysiology of migraine remains unresolved. Support for the hypothesis has been based, to a significant degree, on the fact that some effective antimigraine agents (e.g., ergots and triptans)

inhibit dural NI in animals following trigeminal stimulation.[44] Since the late 1990s, however, various arguments against the involvement of NI in migraine have been developed.[52–58] These arguments are based, to a large degree, on the fact that numerous drugs that block the PPE component of NI in animals have failed to demonstrate antimigraine efficacy in human clinical trials.

An underappreciated fact is that NI consists of two distinct and independent physiological components (i.e., PPE and NV).[59] Drugs that inhibit the release of multiple trigeminal neuropeptides (e.g., SP, NKA, ET3, CGRP) block both the tachykinin-induced PPE and CGRP-induced NV components of NI. Thus, these drugs (e.g., triptans, ergots) are unable to elucidate whether their clinical antimigraine efficacy might derive from the inhibition of both the PPE and NV components of NI, or from an inhibition of only one of the two components of NI.

The NI Theory of Migraine predicts that inhibitors of dural NI in animal models should be effective in the acute treatment of migraine. Neurogenic inflammation, however, consists of two major physiological components: PPE mediated by tachykinins and endothelin 3 and NV mediated predominantly by CGRP effects on vascular smooth muscle. Eight drugs that are inhibitors of PPE, but not NV, in animal models have now been studied in clinical migraine trials. These eight drugs utilize at least three distinct molecular pharmacological mechanisms of action. None of these drugs have been reported to be effective in the acute treatment of migraine. By contrast, a single drug that inhibits CGRP-induced NV has been shown to be effective in the acute treatment of migraine.[60] Therefore, based on these numerous human clinical studies, it can now be concluded that the ability of drugs to selectively inhibit dural PPE in rodents has no predictive value in the acute treatment of migraine.[59] However, the NV component of NI remains a molecular pathway that may play a key role in migraine pathophysiology.

The Sympathetic Nervous System in Migraine

A wide variety of diagnostic tests and clinical signs indicate that migraine shares many features with other chronic sympathetic nervous system (SNS) disorders. Indeed, the fact that sympathetic dysfunction is present in migraine has been noted by many investigators for more than 150 years and has been confirmed in a recent population study.[61] In the mid-nineteenth century, the vasoconstrictive aspect of migraine was attributed to an irritation of the cervical sympathetic system whereas the vasodilatation component of migraine was attributed to a paralysis of the cervical sympathetic system. Numerous other investigators have suggested that a disturbance of the autonomic nervous system is a primary characteristic of migraine.[62]

How could a migraine attack occur as a result of SNS dysfunction if the SNS in migraineurs is anatomically intact? Although norepinephrine (NE) is the neurotransmitter most frequently associated with the SNS, it is only one of many cotransmitters. Dopamine (the immediate chemical precursor of NE), adenosine triphosphate (ATP), neuropeptide Y, dynorphin, and prostaglandins are other neurotransmitters released from sympathetic neurons.[63,64] Moreover, physiological studies have demonstrated variations in the relative amounts of NE versus the other sympathetic cotransmitters that are released from the SNS at different levels of activation. Thus, prolonged stimulation of the SNS depletes NE stores rapidly and leads to an increase in the neuronal release of dopamine (the immediate chemical precursor of NE), ATP, adenosine, and prostaglandins.

Many of the symptoms of an acute migraine attack can be attributed to elevations in the sympathetic cotransmitters (i.e., dopamine, ATP, adenosine, and prostaglandins) as well as to a deficiency of norepinephrine. For example, nausea, vomiting, and yawning have been related to excessive dopamine levels,[65] an increase in pain sensitivity, and inflammation is clearly induced by prostaglandins and sedation has been associated with elevated adenosine levels. Lack of NE leads directly to vasodilatation, ptosis, and other orthostatic symptoms.

It has therefore been proposed that the primary symptoms of migraine are caused by the differential release, following excessive SNS stimulation, of sympathetic *cotransmitters*.[62] Sympathetic activation is a primary component of the physiological stress response. Stress is the most commonly cited cause of migraine. Thus, the SNS offers an unequivocal link between known causes of migraine and a specific biological system. Specifically, it is proposed that a migraine attack may occur when NE release from sympathetic terminals is decreased by prolonged or excessive SNS stimulation at the same time as the concurrent release of dopamine, adenosine, and prostaglandin is increased from the SNS.

This hypothesis is consistent with the observations of Wolff and colleagues. Approximately 24 hours prior to a headache, vasoconstriction is the predominate vascular state of the extracranial vasculature and was noted by Wolff to be “frequently maximal during the minutes preceding the onset of the headache.”[18] The vascular theory of Wolff attributed the vasoconstrictor phase of the migraine prodrome to neuronal release of NE, which than acted on vascular alpha-adrenergic receptors and caused the vasoconstriction. By contrast, the painful phase of migraine was attributed to a painful vasodilatation of extracranial arteries.[16]

However, an adequate physiological explanation was never developed by Wolff to account for the transition from the nonpainful vasoconstriction phase of migraine to the subsequent painful vasodilatation phase. However, it is proposed that at some point in the process of prolonged or excessive SNS stimulation, the relative synaptic concentrations of sympathetic cotransmitters that cause vasoconstriction (i.e., NE) and that cause vasodilatation (i.e., dopamine, ATP, adenosine, prostaglandins) change so that the net effect of SNS stimulation on the extracranial circulation is no longer vasoconstriction but vasodilatation.[62]

Furthermore, this hypothesis is also consistent with a major role for the trigeminovascular system in migraine. The direct relationship that exists between the SNS and the trigeminovascular system is underappreciated in the medical literature. The sympathetic system, both peripherally via the superior cervical ganglia and centrally via the locus coeruleus, provides a major inhibitory input to the trigeminal system. At the vasculature level, activation of the trigeminal system causes a net vasodilatation in the extraparenchymal cranial circulation. By contrast, activation of the SNS in the same vascular distribution causes a net vasoconstriction (under normal conditions). Thus, the vasoactive roles of the SNS and trigeminal system are normally in opposition. Therefore, loss of SNS function, specifically NE, would lead to extracranial vasodilatation and trigeminal activation (as a result of the normal inhibitory effect of the sympathetic system).

Therapeutically, this hypothesis is consistent with current acute pharmacological approaches to migraine. For example, the decrease in the vasoconstrictive effect of NE can be replaced by vasoconstrictors such as ergots and triptans. In addition, it is well established that migraine can also be treated effectively by blocking the increase in the vasodilatory effects of dopamine, prostaglandins, and adenosine. Of note is the fact that each of these effective, yet mechanistically distinct, therapeutic approaches can be related directly to the current pathophysiological hypothesis.

Conceivably, genetically based differences in the population could result in variations in an individual’s ability to synthesize, store, release, and/or re-accumulate NE within the SNS nerve terminals, both centrally and peripherally. Variations in degrees of SNS activation could also cause central and/or peripheral depletion of NE in certain individuals. Future studies are needed to more clearly determine the roles of SNS cotransmitters in the pathophysiology of migraine.

Other Hypotheses

Many other theories have been proposed to explain migraine pathogenesis including alterations in various neurotransmitter systems (e.g., 5-hydroxtryptamine, dopamine, glutamate, nitric oxide, opioids), anatomical structures (e.g., the raphe system, vasculature) and the autonomic nervous system.[66–70]

Conclusion

To date, no single hypothesis has been able to provide an explanation for:

- the multisystemic clinical symptomatology of both the migraine prodrome and the attack;
- the biochemical changes that have been observed in migraineurs between attacks, during the prodrome, and the during the attack;
- a common mechanism of action for diverse migraine triggers such as stress, hormonal changes, tyramine, reserpine, and so forth;

- a common basis for the efficacy of the highly diverse group of pharmacological agents used in the acute (e.g., 5-HT1 agonists, dopamine antagonists, anti-inflammatory agents, caffeine) and prophylactic (e.g., beta-adrenergic antagonists, tricyclic antidepressants) treatment of migraine; and
- the identification of novel therapeutic approaches to migraine based on an understanding of the pathophysiological basis of the disorder.

Clinical features of migraine

Migraine without Aura (Common Migraine)

Migraine without aura (previously called common migraine) is by far the more frequent type of vascular headache. The IHS criteria for migraine without aura include moderate to severe head pain, pulsating quality, unilateral location, aggravation by walking stairs or similar routine activity, attendant nausea and/or vomiting, photophobia and phonophobia, and multiple attacks, each lasting 4–72 hours. There are no focal neurological disturbances preceding the headache.

Migraine with Aura (Classic Migraine)

Migraine with aura (previously called classic migraine) is a vascular headache associated with characteristic premonitory sensory, motor, or visual symptoms. Focal neurological disturbances are common during both the headache attacks as well as prodromal symptoms. Identical focal neurological disturbances without headache or vomiting can also occur and have been termed migraine equivalents or accompaniments. Complicated migraine is a term used to describe migraine with significant transient focal neurological deficits and/or a migraine attack that results in a persisting residual neurological deficit.

The most common premonitory symptoms reported by migraineurs are visual, arising from alterations in occipital lobe function. Scintillating scotomas occur in about one-sixth of migraineurs and usually appear initially in the central portions of the visual fields. A highly characteristic syndrome occurs in which a very small paracentral scotoma slowly expands into a C shape. Highly luminous and scintillating angles appear at the outer edge of the visual alteration. The scotoma expands and moves toward the periphery of the involved half of the visual field over the course of 20–25 minutes. This phenomenon is pathognomonic for migraine and it has never been described in association with a cerebral structural anomaly. It is commonly referred to as a fortification spectrum because the serrated edges of the visual alteration resembles a fortified town.

Basilar Migraine

Migraine attacks may also involve disturbances in brainstem function such as vertigo, dysarthria, or diplopia. Bickerstaff noted attention to a stereotyped sequence of neurological events, often including total blindness and sensorial clouding.[71] The syndrome is believed to be most common in adolescent women. These episodes begin with total blindness and are accompanied or followed by vertigo, ataxia, dysarthria, tinnitus, and/or distal and perioral paresthesias. In many patients, a confusional state also occurs. The neurological symptoms usually persist for 20–30 minutes and are generally followed by a throbbing occipital headache. A confusional state may persist for as long as five days but complete recovery usually occurs.

Treatment of migraine

Nonpharmacologic Approaches

Migraine can often be managed to some degree by a variety of nonpharmacological approaches (Table 4–2). Stress reduction techniques should be used routinely by migraineurs since they provide a simple, cost-effective approach to migraine management.[72] Patients with migraine do not necessarily encounter more stress than headache-free individuals yet they display an intrinsic physiological hyperresponsiveness to stress. Since the stresses of everyday life cannot be eliminated, lessening an individual's response to stress by various techniques is helpful for many patients. Classical and effective relaxation techniques include yoga, transcendental meditation, and conditioning techniques such as biofeedback. For many patients, this approach is a beneficial adjunct to pharmacotherapy. Perhaps even more importantly, avoidance of migraine trigger factors may also provide significant prophylactic benefits. While these measures rarely prevent all migraine attacks, they do seem to lessen both the frequency and severity of attacks.

Table 4–2 Nonpharmacoligical Approaches to Migraine
Identify and then avoid trigger factors such as:
Alcohol (e.g., red wine)
Foods (e.g., chocolates, certain cheeses, monosodium glutamate, nitrite containing foods)
Hunger (avoid missing meals)
Irregular sleep patterns (both lack of sleep and excessive sleep)
Organic odors
Sustained exertion
Acute changes in stress levels
Miscellaneous (glare, flashing lights)
Attempt to manage environmental shifts such as:
Time zone shifts
High altitude
Barometric pressure changes
Weather changes
Assess menstrual cycle relationship





Acute Pharmacological Treatment of Migraine

At present, more than 100 different analgesic medications, encompassing nearly every possible route of administration, are available to treat migraine. Clear and objective rationales can be used to select the most appropriate regimen in a given patient. Indeed, a number of treatment guidelines have been proposed.[73,74] It is now generally agreed that patient satisfaction with migraine therapy depends on obtaining rapid and complete resolution of pain and preventing headache recurrence, thus making two hour pain free and sustained pain free rates more relevant clinical endpoints than the two hour pain relief measure that was used to develop acute migraine drugs in the 1990s.

Many treatment guidelines recommend a step-care approach to migraine management in which a simple analgesic is used first, followed by various combination analgesics and withholding migraine-specific drugs (e.g., ergots, triptans) until the patient has demonstrated an inadequate response to the nonspecific treatments. An alternative approach has been termed the stratified-care approach in which the initial treatment is selected according to the individual's migraine severity and associated disability. This regimen promotes the use of migraine-specific treatments as first-line agents for patients with disabling migraines. However, in reality, these patients have most likely tried and failed to achieve adequate therapeutic response with simple analgesics. The actual clinical distinction between step care and stratified care is therefore minimal.

With any therapeutic approach, it is generally agreed that treatment during mild headache pain improves treatment success rates compared with treatment delayed until the pain is moderate to severe. In general, an adequate dose of whichever agent is chosen should be used as soon as possible after the onset of an attack. If additional medication is required within 60 minutes because symptoms have not yet abated or have returned, the initial dose should be increased for subsequent attacks. As scientific and clinical knowledge expands in the future, the goal for every patient should be to constantly refine and personalize existing therapeutic approaches until regimens are identified that provide rapid, complete, and consistent relief of an acute migraine attack with minimal side effects.

The mainstay of pharmacological therapy is the judicious use of one or more of the many drugs that are effective in migraine. Migraine can be treated pharmacologically using an acute, prophylactic, or combined medication program. The selection of the optimal regimen for a given patient depends on a number of factors such as headache frequency and severity, age of the patient, previous history of medication response, contraindications, drug interactions, and potential side effects. In addition, the presence of other types of headache (e.g., muscle contraction, cluster, etc.) should be evaluated to determine the optimal therapeutic approach. A key determinant in the pharmacological management of migraine is the severity of a given attack (Table 4–3).

Table 4–3 A Staged Approach to Migraine Pharmacotherapy

Stage	Diagnosis	Therapies
Mild migraine	Occasional throbbing headaches; No major impairment of functioning	Acetaminophen, aspirin, NSAIDs; Combination analgesics; Oral 5-HT1 agonists
Moderate migraine	Frequent moderate or severe headaches; Nausea common; Impairment of functioning	NSAIDS + Oral, nasal or SC 5-HT1 agonists
Severe migraine	Significant functional impairment; Marked nausea and/or vomiting	SC, IM or IV 5-HT1 agonists; IM or IV dopamine antagonists; Prophylactic medications if more than 3 times per month severe headaches

Selection of the appropriate therapeutic approach should be guided by a detailed assessment of migraine frequency and severity. Mild migraine is characterized by occasional throbbing headaches with no impairment in functioning and can be treated with mild analgesics or a combination of analgesics. Moderate migraine, defined as the existence of moderate to severe headaches with nausea and leading to some impairment of functioning, should be treated with acute medications that are selective for migraine such as 5-HT1 agonists (e.g., ergots and triptans). Thus, for the vast majority of migraine sufferers, a simple analgesic that may, by necessity on occasion, be supplemented

with a 5-HT1 agonist should prove adequate to manage the disorder.

The most severe form of migraine requires the use of prophylactic agents in addition to acute therapeutic agents and antiemetics. The majority of drugs that have been shown to be effective in the acute treatment of migraine are members of one of three major pharmacological classes: anti-inflammatory agents, 5-HT1 agonists, and dopamine antagonists. The classes of available agents are summarized here while the specific agents are listed in Table 4–4.

Table 4–4 Drugs Effective in the Acute Treatment of Migraine

Drug	Trade Names	Dosage
NSAIDs		
Aspirin	generic	650–1000 mg
Diclofenac	generic	50–100 mg
Ibuprofen	generic	400–800 mg
Naprosyn	generic	500–1000 mg
Acetaminophen	generic	1000 mg
Combination NSAID Products		
Aacetaminophen, aspirin, caffeine	Excedrin Migraine	Two tablets or caplets every 6 h (max 8/d)
Acetaminophen,	Midrin*	Two capsules at onset
Isometheptene, Dichloralphenazone	followed by 1 capsule	q 1 h (max 5 capsules)
Acetaminophen, Butalbital	Phrenilin*	One or 2 tablets q 4 h (max 6 capsules)
Acetaminophen, Butalbital, caffeine	Fioricet*	One or two tablets q 4 h (max 6 capsules)
Aspirin, caffeine, Butalbital	Fiorinal*	One or 2 tablets q 4 h Butalbital (max 6 tablets)
Aspirin, Butalbital	Axotal*	One tablet q 4 h (max 6 tablets)
5-HT1 agonists		
Oral		
almotriptan	Axert	12.5 mg tablet at onset may repeat initial dose after 2 h (max 25 mg/d)
eletriptan	Relpax	40 mg tablet at onset may repeat initial dose after 2 h (max 80 mg/d)
ergotamine	Ergostat, Ergomar	One sublingual tablet at onset and q 1/2 h (max 3/d, 5/wk)
frovatriptan	Frova	2.5 mg tablet at onset may repeat initial dose after 4 h (max 7.5 mg/d)
naratriptan	Amerge	2.5 mg tablet at onset; may repeat once after 4 h (max 5 mg/d)
rizatriptan	Maxalt, Maxalt-M LT	5–10 mg tablet at onset; may repeat after 2 h (max of 30 mg/d)
sumatriptan	Imitrex	50–100 mg tablet at onset; may repeat after 2 h (max 200 mg/d)
zolmitriptan	Zomig, Zomig Rapimelt	2.5 mg tablet at onset; may repeat after 2 h (max 10 mg/d)
Nasal		
dihydroergotamine	Migranal Nasal Spray	Prior to nasal spray, the pump must be primed 4 times; one spray (0.5.mg) per nostril is administered followed, in 15 min, by a second spray per nostril
sumatriptan	Imitrex Nasal Spray	5–20 mg spray as 4 sprays of 5 mg per nostril or a single 20 mg spray (may repeat once after 2 h, not to exceed a dose of 40 mg/d)
zolmitriptan	Zomig Nasal	5 mg spray may repeat once after 2 h (max 10 mg/d)

	Spray	
Parenteral		
dihydroergotamine	D.H.E. 45	1 mg IV, IM, or SC at onset and q 1 h (max 3 ml/d, 6 ml/wk)
sumatriptan	Imitrex Injection	6 mg SC at onset (may repeat once after 1 h for maximum of two 6 mg injections in 24 hours)
Combination 5-HT1 Agonist Products		
Oral		
Ergotamine, Caffeine	Cafergot, Wigraine Ercaf	Two tablets at onset then one tablet q 1/2 h (max 6/d, 10/wk)
Ergotamine,	Cafergot P-B;	One suppository at onset then one hour later (max 2/d or 5/wk)
Caffeine,	Wigraine P-B	
Belladonna,	Pentobarbital	
Dopamine Antagonists		
Parenteral		
Chlorpromazine	generic*	0.1 mg/kg IV at 2 mg/min (max 35 mg/d)
Metoclopramide	Reglan,* generic	10 mg IV
Prochlorperazine	Compazine,* generic*	10 mg IV

* Not specifically indicated by the FDA for migraine.

Acetaminophen, aspirin, and nonsteroidal anti-inflammatory agents (nsaids)

Since approximately half of migraine sufferers are undiagnosed, it is reasonable to conclude that the majority of migraine attacks are treated solely with mild analgesics such as acetaminophen, aspirin, or NSAIDs (Table 4–4). Indeed, this class of agents can reduce significantly both the severity and duration of a migraine attack. Acetaminophen and aspirin, for example, have been used in migraine treatment for over 50 years and probably remain the drugs used most frequently in acute therapy.[75] In addition, a number of NSAIDs (e.g., ibuprofen, diclofenac, naproxen) have been shown to be similarly effective. The efficacy of acetaminophen in migraine is of theoretical importance since this agent is analgesic but not anti-inflammatory (as opposed to the other agents in this class). Ibuprofen (as a monotherapy) and the combination of acetaminophen, aspirin, and caffeine (e.g., Excedrin Migraine) have been approved for use by the FDA for the treatment of mild to moderate migraine. Diclofenac has been approved for the acute treatment of migraine in other countries. The combination of aspirin and metoclopramide, in a European study, has been show to be equivalent to a single dose of sumatriptan.[76] Major side effects of NSAIDs include dyspepsia and gastrointestinal irritation.

A number ofnon-narcotic combination analgesic preparations have been developed for use in migraine. In general, each preparation contains a combination of aspirin or acetaminophen with a mild vasoconstrictor (e.g., isometheptene) or a sedative (e.g., butalbital). The combination of acetaminophen, dichloralphenazone, and isometheptene (i.e., Midrin, Duradrin, generic), 1 to 2 capsules, has been approved for use in vascular headaches such as migraine in the United States. Since the clinical studies demonstrating the efficacy of this combination analgesic in migraine predated the clinical trial methodologies used with the triptans, it is difficult to assess the clinical efficacy of this sympathomimetic compound in comparison to other agents. These preparations are contraindicated in patients with glaucoma and/or severe cases of renal disease, hypertension, organic heart disease, and hepatic disease, and with concurrent use of monoamine oxidase (MAO) inhibitors. Butalbital is a short-acting to intermediate-acting barbiturate that is marketed in the United States in combination with aspirin or acetaminophen or other agents. Butalbital-containing preparations (e.g., Fiorinal) can be very effective in migraine when used judiciously. This combination product remains a commonly used migraine therapeutic in the United States. The major concern with these compounds is the addictive potential of butalbital. Patients should be advised to limit the use of these compounds to the FDA-approved dosage of no more than six tablets daily, although many physicians recommend that use be limited to no more than two tablets per day. These preparations are FDA-approved for muscle contraction headaches, but are also used to treat relatively mild migraine.

As with all other migraine therapeutics, a general consensus is that these therapeutic agents are most effective when taken early in the migraine attack. Mild analgesics should be taken at the first sign of the onset of an acute attack and then as directed until the headache is completely relieved. However, as mentioned previously, the effectiveness of these agents in migraine is usually less than optimal in more moderate or severe migraine attacks.

5-HT1 Agonists

Oral ergotamine ergot derivatives were first found to be effective antimigraine agents in the 1920s and they continue to be a major class of therapeutic agents for the acute relief of moderate or severe migraine. Ergots are nonselective pharmacological agents in that they interact with numerous neurotransmitter receptors, including all known 5-HT1 and 5-HT2 receptors as well as adrenergic and dopaminergic receptors.[77] The use of ergots for migraine is appropriate for patients with frequent moderate migraine or infrequent severe migraine attacks. Ergot preparations can be taken orally, sublingually, rectally, intramuscularly, intravenously, or via inhalers. As with other medications used to treat migraine, the patient should be advised to take ergot preparations as soon as possible after the onset of a migraine attack. Nausea and vomiting occur in approximately 10% of patients after oral administration of ergotamine.

Gastrointestinal absorption of ergot alkaloids is erratic, a fact that may explain the large variation in patient response to these drugs.[78] The coadministration of caffeine has been reported to increase intestinal absorption of ergotamine, which provides a rationale for the use of combination oral preparations containing the two agents.[79] Various preparations of ergot alkaloids are available, most of which contain additional ingredients, such as caffeine and/or barbiturate derivatives (Table 4–4). Except for a sublingual formulation of ergotamine (Ergomar), oral formulations of ergotamine also contain 100 mg caffeine. The average oral ergotamine dose for a migraine attack is 1–2 mg. Since the clinical studies demonstrating the efficacy of ergotamine in migraine predated the clinical trial methodologies used with the triptans, it is difficult to assess the clinical efficacy of

ergotamine versus the triptans. In general, ergotamine appears to have a much higher incidence of nauseating side effects but less headache recurrence.

With ergotamine preparations, a 1-mg or 2mg dose should be taken at the onset of the headache and followed by as many as 4 additional 1-mg tablets, each taken 30 minutes apart. A patient should not take more than 10 mg per week of ergotamine. Of concern is the fact that ergotamine causes prolonged vasoconstriction. The administration of doses greater than 1 mg per day may cause peripheral vasospasm and can, rarely, lead to serious side effects such as gangrene.[78] Ergots should not be taken within 24 hours of the use of triptans (based on the theoretical additive pharmacological effects of the drugs). It also is recommended that ergot alkaloids not be used in complicated migraine.

Oral triptans

The introduction of triptans for the acute treatment of migraine in the 1990s led to significant progress in preclinical and clinical research on migraine. At the scientific level, the selective pharmacological effects of triptans at 5-HT1 receptors led to new insights into the pathophysiology of migraine. At the clinical level, triptans add an additional class of effective acute antimigraine agents to the therapeutic management of migraine. Their ability to decrease, rather than exacerbate, the nausea and vomiting of migraine represents an important advance in the treatment of the condition. The introduction of triptans also refocused attention of the role of 5-HT in migraine. It is now clear that stimulation of 5-HT1 receptors, and more specifically the 5-HT1B receptor subtype, can acutely stop a migraine attack. A variety of triptans are now available for the treatment of migraine (Table 4–4). In general, the triptan class of drugs has similar pharmacological properties and the drugs display similar clinical efficacy. Although large scale comparative clinical trials have never been performed, a number of meta-analyses have been completed in an attempt to determine the best triptan.[80–82]

Overall, differences between the triptans are relatively minor such that no clear and unequivocal best can be selected. As shown in Table 4–5, the reported clinical efficacy of the seven currently available oral triptans does not have any obvious relationship to their potency, half-life, or bioavailability. The only pharmacokinetic factor of potential significance appears to be the Tmax (i.e., time to peak plasma level). Naratriptan and frovatriptan are the slowest acting members of the triptan class and they also display the lowest efficacy at the two-hour time point. This observation is in keeping with a significant body of data indicating that faster-acting analgesics are more efficacious than slower acting agents (Table 4–5).

Table 4–5 Comparative Pharmacology of Oral Triptans

Drug	Trade Name	Typical Dose (h)	Tmax (mg)	$t_{1/2}$ (h)	Oral Bioavailabilty (%)	Clinical Efficacy at 2 h (%)
almotriptan	Axert	12.5	1–3	3–4	70	60
eletriptan	Relpax	40	1.5–2	4	50	61
frovatriptan	Frova	2.5	2–4	26	25	40
naratriptan	Amerge	2.5	2–4	5–6	68	45
rizatriptan	Maxalt	5	1–1.5	2–3	45	62
sumatriptan	Imitrex	50	2–3	2	14	61
zolmitriptan	Zomig	2.5	2	2.5–3	44	65

Data adapted from the FDA-approved package inserts.

Another important clinical issue to consider is that monotherapy using selective oral 5-HT1 agonists does not result in rapid, consistent, and complete relief of migraine in all patients. To an unbiased observer, it is clear that the initial promise that triptans might prove to be a panacea for migraine has not been fulfilled although they do seem to offer equivalent or slightly higher rates of pain free efficacy at the two-hour time point than traditional antimigraine medications. In addition, the drugs are not effective in migraine with aura unless given after the aura is completed and the headache initiated. Side effects, often transient and mild, occur in as many as 89% of patients. Recurrence of headache has been cited as the major limitation and occurs in 40%–78% of patients, at least occasionally. Moreover, 5-HT1 agonists are contraindicated in individuals with a history of cardiovascular disease. Since the goal of acute migraine management is to achieve rapid, consistent, and complete relief of symptoms in as many patients as possible, then it must be accepted that 5-HT1 agonist monotherapy using triptans is inadequate for many migraine sufferers.

Nasal 5-HT1 agonists

The fastest acting nonparenteral antimigraine therapies that can be self-administered include nasal formulations of dihydroergotamine (Migranal), sumatriptan (Imitrex Nasal), and zolmitriptan (Zomig Nasal Spray). The nasal sprays result in substantial blood levels within 30 to 60 minutes. However, the nasal formulations suffer from inconsistent dosing, poor taste, and variable efficacy. Although in theory, the nasal sprays might provide faster and more effective relief of a migraine attack than oral formulations, their reported efficacy is only approximately 50%–60%, most likely due to the fact that a significant amount of the dose is actually swallowed and absorbed in the gastrointestinal tract rather than nasally.

Parenteral 5-ht1 agonists

The rapid relief of a moderate or severe migraine attack can often be achieved by parenteral administration of drugs such as dihydroergotamine (D.H.E. 45 Injectable) or sumatriptan (Imitrex SC). Both are approved for such use by the FDA. Peak plasma levels of dihydroergotamine are achieved 3 minutes after intravenous dosing, 30 minutes after intramuscular dosing and 45 minutes after subcutaneous dosing. If an attack has not already peaked, subcutaneous or intramuscular administration of 1 mg DHE suffices for about 80%–90% of patients. Sumatriptan 6 mg SC is effective in approximately 70%–80% of patients, reaching maximal plasma levels in approximately 15 minutes.

The use of intravenous ergots has been recommended for the treatment of severe migraine. In a landmark study of acute migraine patients, 49 of 55 patients were reported to be headache-free within 48 hours after receiving 0.5 mg of dihydroergotamine and 10 mg of metoclopramide every 8 hours.[83] Nausea and vomiting occur in approximately 20% of patients after parenteral administration of ergots. This side effect is problematic, since nausea and sometimes vomiting are often part of the symptomatology of severe migraine attacks.

Dopamine antagonists

Oral dopamine antagonists have not been documented to be effective in the acute treatment of migraine but may be useful as concurrent therapeutics in migraine with moderate or severe nausea. By contrast, parenteral dopamine antagonists (e.g., chlorpromazine, prochlorperazine, metoclopramide) can provide significant acute relief of migraine.[65] In addition, parenteral dopamine antagonists can be used in combination with parenteral 5-HT1 agonists.[83]

Opioids

Opioids are unequivocally effective in the acute treatment of migraine. For example, intravenous meperidene (Demerol), generally in the range of 50–100 mg, is given frequently in the emergency room. A nasal preparation of butorphanol is available for the treatment of acute pain. As with all opioids, the use of nasal butorphanol should be limited to a select group of migraineurs. Opioids work in the sense that the pain of migraine is eliminated. However, opioids are clearly suboptimal in patients with recurrent headache for two major reasons. First, opioids do not treat the underlying headache mechanism. Rather, they act at the thalamic level to alter pain sensation. Second, the recurrent use of opioids to traet acute migraine attacks can lead to significant problems. In patients taking oral opioids such as oxycodone (e.g., Percodan, Oxycontin) or hydrocodone (e.g., Vicodin, Lortab), opioid addiction can greatly confuse the treatment of migraine. The headache that results from opioid craving and/or withdrawal can be difficult to distinguish from chronic migraine. Therefore, it is recommended that opioid use in migraine be limited to patients with severe, but infrequent, headaches that are unresponsive to other pharmacological approaches.

Prophylactic Treatment of Migraine

A general consensus among neurologists is to treat prophylactically patients having three or more migraines per month if the pain intensity is moderate or severe. A variety of agents (discussed here) are effective in the prophylactic treatment of migraine, although none are effective in greater than 50%–70% of patients (Table 4–6). The agents must be taken routinely and daily compliance needs to be stressed, even in the absence of headache. Prophylactic medications should be given for a period of at least 6–12 weeks before being considered ineffective.

Table 4–6 Drugs Effective in the Prophylactic Treatment of Migraine

Drug	**Trade Name**	**Dosage**
Beta-adrenergic agents		
Propranolol	Inderal Inderal LA	80–320 mg qd
Timolol	Blocadren	10–60 mg qd
Atenolol	Tenormin*	50–100 mg qd
Nadolol	Corgard*	40–160 mg qd
Metoprolol	Lopressor*	50–400 mg qd
Anticonvulsants		
Topiramate	Topamax	25–200 mg qd (max 200 mg/d)
Valproic acid	Depakote	250–600 mg bid (max 1000 mg/d)
Serotonergic drugs		
Methysergide	Sansert	2–8 mg q d
Cyproheptadine	Periactin*	4–16 mg q d
Tricyclic antidepressants		
Amitriptyline	Elavil,* generic	10–150 mg qhs
Nortriptyline	Pamelor,* generic	25–150 mg qhs
Monoamine oxidase inhibitors		
Phenelzine	Nardil*	15 mg tid
Isocarboxazid	Marplan*	10 mg qid
Other		
Flunarizine	Sibelium* (Europe only)	5–10 mg qhs
Coenzyme Q10	generic*	100 mg tid
Petasites hybridus	Petadolex*	75 mg bid



* Not specifically indicated by the FDA for migraine.

If found to be effective, the medications should be continued for six months and then discontinued due to the high incidence of remission in migraine. Many patients are able to discontinue medication and experience fewer and milder attacks for long periods, suggesting that these drugs may alter the natural history of migraine. If headache recurs after discontinuation of prophylactic therapy, the medication regimen should be reinstituted for another six-month trial if frequent headaches return.

The mechanism of action of migraine prophylactic drugs remains uncertain. Suppression of cortical spreading depression (CSD) may be a common pharmacological effect of migraine prophylactic agents, based on a study in rats.[84] Multiple daily treatments with betablockers, valproate, topiramate, methysergide, or amitriptyline reduce the number of potassium-evoked cortical spreading depressions and elevated the electrical stimulation threshold for the induction of cortical spreading depression in rats, whereas acute treatment is ineffective. Longer treatment durations produce stronger CSD suppression. Ayata and colleagues[84] concluded that these data suggest that the suppression of CSD

provides a common pharmacological effect of migraine prophylactic drugs.

Drugs that have been FDA approved for the prophylactic treatment of migraine include propranolol, timolol, topiramate, valproic acid, and methysergide. In addition, a number of other drugs appear to display prophylactic efficacy migaine. This second group of drugs includes amitriptyline, nortriptyline, flunarizine, verapamil, and cyproheptadine. Methysergide is usually reserved for recalcitrant cases because of its serious potential side effects (i.e., retroperitoneal or cardiac valvular fibrosis as noted here).

Beta-adrenergic Receptor Antagonists. A serendipitous finding in patients with exertional angina was that propranolol was able to prevent frequent migraine attacks.[85] Multiple clinical studies have shown that approximately 50%–70% of patients derive some benefit from prophylactic propranolol therapy. Approximately one-third of migraine patients report a greater than 50% reduction in the number of attacks with treatment. A dose of 40 mg twice a day usually is begun with as much as 320 mg per day being given for at least 6–12 weeks before deciding that the patient is non-responsive to therapy. Several other beta-adrenergic antagonists have been used in the treatment of migraine.[86] Atenolol, metoprolol, nadolol, bisoprolol, and timolol appear to be at least as effective as propranolol in migraine prophylaxis. Only propranolol and timolol, however, are approved by the FDA for use in the prophylactic treatment of migraine in the United States. More variable results have been obtained with pindolol and a number of other beta-adrenergic antagonists (e.g., acebutolol, oxprenolol, alprenolol) do not appear to be effective in migraine therapy.

The pathophysiological basis for the effectiveness of beta-adrenergic antagonists is not known. No single pharmacological property of this class of drugs can explain their apparent clinical efficacy.[78] Antimigraine effects of these drugs do not correlate with their potency at beta-adrenergic receptors, since not all beta-adrenergic receptor antagonists are effective antimigraine agents. Alternatively, it has been suggested that only pure beta-adrenergic antagonists are effective agents in migraine therapy, whereas antagonists that display “intrinsic sympathomimetic activity” (i.e., partial agonist activity) may be less effective migraine prophylactic agents.[86,87] Side effects with beta-adrenergic receptor antagonists are mild. Common side effects include lethargy, gastrointestinal upset, and orthostatic hypotension, although these side effects rarely necessitate discontinuation of the drug. Exercise intolerance and potential for impotence do limit the acceptability of these drugs to males, particularly young males. These drugs are contraindicated in asthma, advanced AV block, sinus bradycardia, and diabetes mellitus.

Antiepileptic drugs

Antiepileptic drugs (AEDs) have been shown to be effective in the prophylactic treatment of migraine and are reasonably well tolerated. The precise mechanisms of action of AEDs in migraine prophylaxis are not fully understood.[88] In general, however, AEDs inhibit neuronal hyperexcitability and it is believed that this ability may underlie their efficacy in the prophylactic treatment of migraine. Their efficacy is most likely mediated by the inhibition of excitatory glutaminergic neurotransmission and/or the potentiation of inhibitiory γ-aminobutyric acid (GABA) neurotransmission. Selection of the most appropriate agent for an individual patient requires an assessment of the pharmacodynamics, tolerability, and safety of each agent.

Topiramate (Topamax®) is a widely used antiepileptic agent that is structurally different from other AEDs.[89] It was developed initially as an antidiabetic drug. Topiramate exerts an inhibitory effect on sodium conductance, decreasing the duration of spontaneous bursts and the frequency of generated action potentials, enhances GABA by unknown mechanisms, inhibits the AMPA subtype glutamate receptor, and is a weak inhibitor of carbonic anhydrase. In the United States, it currently is approved for (1) partial onset and secondarily generalized tonic-clonic seizures, (2) primary generalized tonic-clonic seizures, (3) Lennox Gastaut syndrome, and (4) migraine.

In migraine prophylaxis, topiramate should be started at a low dose and titrated slowly to prevent adverse effects.[90,91] The recommended starting dose is 25 mg/day and can be increased in weekly or biweekly increments of 25–50 mg. For migraine prophylaxis, a stable daily dose of 25–100 mg is typical although doses at high as 200 mg/day have been used. The most common adverse effects of topiramate include ataxia, impairment of concentration, confusion, dizziness, fatigue, paresthesias in the extremities, somnolence, disturbance of memory, depression, agitation, and slowness of speech. However, tolerance to these side effects often develops and it is recommended that the patent be titrated over the course of a few weeks. When the drug is discontinued, these adverse effects subside within a few weeks. Unlike nearly all other migraine prophylaxis drugs that are associated with weight gain, topiramate is associated with weight loss in a significant number of individuals.[92]

Valproic acid has shown evidence of efficacy in multiple placebo-controlled migraine prophylaxis trials.[93,94] It has been used in different forms, including divalproex sodium, magnesium or calcium salt, or valpromide. These forms do not differ significantly. Valproic acid enhances GABA function, but this effect is observed only at high concentrations. It may increase the synthesis of GABA and it produces selective modulation of voltage-gated sodium currents during sustained, rapid, repetitive neuronal firing.[95]

The usual starting dose of valproic acid in migraine is 250 mg/day with a maintenance dose of 500–1500 mg/day. The dose can be increased every few days, as tolerated.

A number of adverse events occur with valproic acid. It is generally well tolerated with most adverse events rated as mild to moderate in severity. Dose-related adverse effects include nausea, vomiting (mainly during initiation of therapy and improved by administration of enteric-coated preparations), tremor, sedation, confusion or irritability, and weight gain. Severe sedation or even coma may result from hyperammonemia, typically with normal liver function tests.

5-HT Receptor Antagonists. Serotonergic antagonists such as methysergide represent the first class of drugs shown to be effective in migraine prophylaxis.[96] Methysergide is an ergot derivative that has complex effects on serotonergic and other neurotransmitter systems. It has been shown to be effective in 60%–80% of migraine patients and should be given for at least a six-week trial.[96] Common side effects include nausea, vomiting, and diarrhea. A few patients have developed retroperitoneal or cardiac valvular fibrosis when used for more than eight months, so close monitoring is required for patients using this drug. The risk of the fibrotic complication is about 1:1500 although it is likely to reverse after the drug is stopped. Therefore, it is recommended that methysergide be administered for no more than six consecutive months. The patient should then discontinue the medication for at least four to eight weeks, after which point the drug can be reintroduced safely. Other 5-HT receptor antagonists (i.e., pizotifen, mianserin) also have been reported effective in migraine prophylaxis, but cyproheptadine is the only other serotonergic agent currently available in the United States (although not approved for use by the FDA for migraine prophylaxis).

Tricyclic Antidepressants. Tricyclic antidepressants such as amitriptyline are effective prophylactic agents in migraine. The beneficial effect in migraine is independent of the antidepressant actions.[97–99] Amitriptyline is also used commonly in mixed headache cases (i.e., patients having symptoms of both migraine and muscle contraction headaches). Amitriptyline is a potent blocker of the 5-HT transporter and other transporters and also is an antagonist of multiple neurotransmitter receptors. However, its mechanism of action in migraine prophylaxis is unknown. The drug is not FDA-approved for the treatment of migraine despite its widespread clinical use in this disorder. Patients should be started on a 10-mg or 25-mg dose at bedtime, and the dose may be increased to 150–200 mg/day. Side effects usually are related to the anticholinergic properties of the drug (i.e., dry mouth, dizziness, blurred vision, urinary retention, cardiac arrhythmia). In addition, sedation and weight gain occasionally are encountered and may limit patient compliance. If side effects occur, the dose should be halved. A 6-week to 12-week trial is recommended before the drug is considered ineffective. Amitriptyline may predispose patients to cardiac arrhythmias and is therefore contraindicated in heart disease.

Other. Monoamine oxidase inhibitors such as phenelzine and isocarboxazid have been reported to be effective in migraine prophylaxis.[78] There also is evidence that monoamine oxidase inhibitors are valuable in migraine prophylaxis because of their ability to increase levels of endogenous 5-HT. Frequent side effects include orthostatic hypotension, insomnia, and nausea.

Flunarizine is a relatively weak Ca2+ channel antagonist that is marketed for migraine prophylaxis in Europe.[100-101] The nonsteroidal anti-inflammatory agent naproxen also has been reported to be an effective migraine prophylactic agent.[102] Narcotics definitely are contraindicated in migraine prophylaxis due to their addictive potential.

A variety of natural products have also been reported to be effective in the prophylactic treatment of migraine. The two agents that have been studied most extensively in placebocontrolled trials are Coenzyme Q10[103] and Petasites.[104]

Conclusion

Migraine is a specific neurological syndrome that has a wide variety of manifestations. At the most basic level, migraine without aura can be defined as a throbbing (usually unilateral) headache with associated nausea. A prodromal phase may last as long as 24 hours before the headache and may consist of mood and appetite changes. The headache itself is often accompanied by photophobia, hyperacusis, polyuria, and/or diarrhea. A migraine attack usually lasts from hours to days and is followed by prolonged pain-free intervals. The headache frequency is extremely variable but usually ranges from 1–2 per year to 1–4 per month. The International Headache Society (IHS) has developed specific criteria for the diagnosis of migraine.

At present, more than 100 different medications, encompassing nearly every possible route of administration, are available to treat migraine. Clear and objective rationales can be used to select the most appropriate regimen in a given patient. It is now generally agreed that patient satisfaction with migraine therapy depends on obtaining rapid and complete resolution of pain and preventing headache recurrence, thus making two hour pain free and sustained pain free rates more relevant clinical endpoints than the two hour pain relief measure that was used to develop acute migraine drugs in the 1990s.

There is a general consensus among physicians that patients having three or more moderate or severe migraine attacks each month should be treated with prophylactic therapies. More than 50 pharmaceutical products have been reported to be effective in the prophylactic treatment of migraine. An analysis of clinical trial data indicate that, on average, the frequency of migraine attacks is reduced by ~35%–45% in treated subjects whereas the frequency of migraine attacks with placebo is reduced by ~20%–25%. Relatively small differences are observed between existing therapeutic agents. Selection of the most appropriate agent for an individual patient requires an assessment of the pharmacodynamics, tolerability, and safety of each agent.

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Ischemic Stroke

Chapter: Ischemic Stroke
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The number of new and recurrent cases of stroke exceeds 700 000 annually in the United States. Stroke constitutes the third leading cause of mortality, and is the leading cause of disability among adults in this country. This chapter reviews current clinical and experimental drug therapies for acute ischemic stroke that represents approximately 85% of total strokes. Therapies intended for the primary and secondary prevention of stroke, and hemorrhagic stroke, are not discussed.

Treatment of ischemic stroke presents a formidable challenge. Interventions targeting the known intravascular mechanisms that underlie stroke pathology (thrombolytic, anticoagulant, and antiplatelet therapies) are of demonstrable benefit. Neuroprotective strategies attempting to blunt or reverse cellular mechanisms of tissue damage, although promising in experimental studies, remain clinically unsuccessful. We review in the initial sections the biology of ischemic injury and intravascular mechanisms contributing to clinical stroke, including several important issues in stroke modeling that affect drug development. We then consider specific drug therapies in use or under evaluation for acute stroke, and finally present a current guide to acute stroke management.

Mechanisms of ischemic stroke

Cellular Pathophysiology and Targets for Therapy

The mechanisms underlying ischemic injury in brain are largely those common to all cells and tissues (Figure **5–1**). However, the duration of blood flow disruption that can be tolerated, and the consequences of the resultant injury, are determined by the high metabolic requirement of brain and the spectrum of intrinsic vulnerabilities of diverse cell types. When cerebral blood flow (CBF) falls precipitously, tissue oxygen is depleted within seconds, resulting in rapid disruption of organized neuronal activity[1] and a flattening of the electroencephalogram (EEG).[2] Anaerobic metabolism is activated and sustained, during which time glucose and other substrates are depleted, adenosine triphosphate (ATP) production fails, and the consequent inability to maintain membrane ionic gradients causes widespread cellular depolarization.[34] Delay of reperfusion for minutes to tens of minutes causes a selective loss of neurons and oligodendrocytes with a spatiotemporal pattern that depends on the cell population and brain region affected.[5–7] Longer intervals of global ischemia in brain are not compatible with survival. However, a similar sequence of events takes place within a focal ischemic territory following occlusion of a major cerebral artery. In this environment, astrocytes and vascular elements become progressively stressed as the depth and duration of ischemia increase (typically beyond one hour in experimental models), resulting ultimately in tissue pannecrosis characteristic of an infarct.[8]

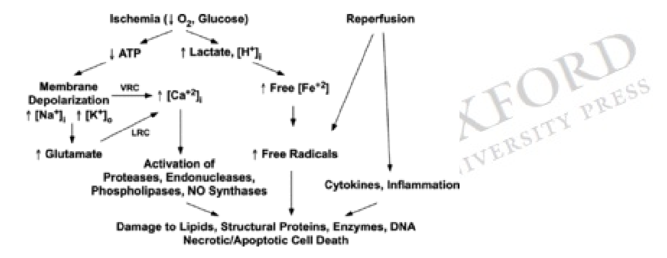




Figure 5–1.
Mechanisms of injury in focal cerebral ischemia. CBF loss results in the primary metabolic events of ATP depletion and tissue acidosis. Cell depolarization and subsequent calcium accumulation trigger cascades of regulatory events, and decreased pH facilitates iron-catalyzed free radical generation, together contributing to multiple potential injury

pathways. Delayed reperfusion can lead to further injury via acute oxidative stress and delayed inflammation. Abbreviation: VRC, voltage-regulated calcium channels; LRC, ligand-regulated calcium channels.

The ischemic penumbra

Of particular importance in a focal ischemic insult is the gradient in CBF deficit that characterizes the compromised vascular territory. This ischemic penumbra that lies between normally perfused brain and the severely ischemic, depolarized core receives intermediate levels of perfusion. The region is functionally silent because neurotransmission is abolished but the area is still viable and can recover if blood flow is restored in a timely fashion.[9,10] The penumbra experiences repeated waves of depolarization,[11,12] each associated with an interval of increased metabolic demand that results in progressive deterioration of ion homeostasis.[13,14] There is also a hemodynamic component to such events. In normal tissue CBF increases to meet the increased metabolic demands of propagated depolarizations, but such blood flow increases are attenuated within an ischemic region.[13,15] Peripheral regions closer to a source of collateral perfusion may take a greater share of CBF in response to depolarization and thus steal from the poorly perfused central core,[16] worsening the ischemic insult and enlarging the region of terminal depolarization.[11] In view of the more prolonged time course of injury in this region, the ischemic penumbra presents the main target for stroke therapy, including both prompt reperfusion and reversal of subsequent injury cascades. Efforts to detect the ischemic penumbra using a combination of CT and CT angiograms or diffusion weighted MRI imaging (DWI) and perfusion weighted MRI imaging (PWI) are encouraging but a method to routinely and definitively detect the true borders of the penumbra has yet to be developed. Nevertheless, the combination of DWI with PWI does hold promise for defining the population of acute stroke patients that should or should not receive thrombolytic therapy (see following).

Reperfusion injury and oxidative stress

Restoring cerebral blood flow in a timely manner is essential for recovery of ischemic tissue and remains the first goal of acute intervention in stroke.[17] However, reperfusion presents additional challenges, especially if it is delayed, because the delivery of blood may subject the injured tissue to additional damage from free oxygen radicals (Figure **5–1**), increased cerebral edema, hemorrhagic transformation, and arrival of inflammatory cells.[18–20] Although all cells possess intrinsic antioxidant defenses and repair mechanisms this presents a primary target for additional therapy. The few antioxidant compounds that have undergone clinical trials have failed to show benefit in stroke, but other trials are ongoing or in the planning stages.

Reperfusion injury per se has been difficult to approach experimentally. Under most conditions infarcts simply increase in size with duration of vascular occlusion, reperfusion becoming progressively less effective with greater delay until the resulting infarct is comparable to that obtained after permanent occlusion.[21] A reported increase in infarct volume after transient compared to permanent occlusion in one rat strain, originally interpreted as a robust model of reperfusion injury,[22] may in retrospect reflect the adverse effects of hypotension during sustained anesthesia.[23] Nevertheless, brief hypothermia coincident with reperfusion can be profoundly protective in experimental stroke,[24,25] with particularly marked attenuation of delayed edema development suggesting specific protection of the vasculature.[26] Clinical imaging studies have also identified acute vascular injury following thrombolytic therapy.[27] This is consistent with earlier results showing a vascular site of superoxide production following ischemia/reperfusion.[28,29] Future studies of interventions targeting reperfusion injury should be designed to temporally coincide with initiation of thrombolytic therapy.

Excitotoxicity

Glutamate is the principal excitatory neurotransmitter in the central nervous system, its several receptors either directly gating calcium or sodium channels, or modulating intracellular calcium release (Figure **5–1**). Elevated glutamate levels can clearly kill neurons both in vivo[30] and in culture.[31] Excitatory amino acids progressively accumulate in brain extracellular space following ischemic depolarization, and an imbalance of excitatory and inhibitory transmitters levels may persist even after recirculation.[32] This has fueled long standing interest in stroke therapies targeting glutamate receptors, and numerous studies in experimental models demonstrated protective effects of the agents developed, the most widely studied being the N-methyl-D-aspartate (NMDA) receptor subtype antagonist, dizocilpine maleate (MK-801). However, unanticipated drug-induced hypothermia ultimately emerged as the key mediator of neuroprotection by such compounds in models of global ischemia.[33–34] Conversely, hemodynamic factors may partially explain the experimental efficacy of NMDA antagonists in experimental stroke since, in addition to suppressing peri-infarct depolarizations[35] and reducing the cerebral metabolic rate,[36] MK-801 globally increases CBF when administered in the absence of anesthesia.[37,38] This would effectively blunt the metabolic challenge to the penumbra, and may underlie the greater efficacy of MK-801 in experimental models with robust collateral perfusion.[39,40] Regardless of the mechanism mediating neuroprotection in experimental stroke, no glutamate antagonist has been successful in clinical trials. To explain the disconnect between preclinical and clinical studies, some investigators have suggested that excitotoxicity is a comparatively acute mechanism that may not be readily accessible to intervention in clinical stroke. Furthermore, glutamate antagonists may offset the potential positive impact of glutamate on intrinsic pathways that control cell survival.[41]

Apoptosis

A prominent candidate mechanism proposed to underlie ischemic injury has been the activation of signals triggering programmed cell death.[42] Although apoptosis per se is detectable after focal ischemia in brain,[43–46] its quantitative contribution to stroke injury remains uncertain. Large scale apoptosis was invoked to explain a phenomenon of slowly progressive tissue loss after brief intervals of focal ischemia,[47] which others, however, have failed to reproduce.[24,48] Oligodendrocytes appear to be the predominant cell type exhibiting classical apoptosis after transient global ischemia,[5] and their vulnerability is increasingly appreciated as a contributor to outcome after focal ischemia,[49] offering another potential target for stroke therapy.

Intrinsic neuroprotective mechanisms

Multiple signaling mechanisms and structural elements are potentially impacted secondary to depolarization, calcium influx, and oxidative injury (Figure **5–1**). Such responses include cascades of enzyme activation and inactivation and cytoskeletal changes,[50] DNA damage,[51,52] protein aggregation and degradation,[53] global depression of protein synthesis,[54,55] and select changes in gene expression,[56,57] many components of which are mechanistically linked.[58] Notable among the consequences of ischemic insults are potentially protective effects on pathways affecting antioxidant mechanisms,[57] growth factors,[59,60] chaperone function,[57,58] and DNA repair.[61] Approaches to enhance such intrinsic mechanisms that may facilitate cellular recovery remain under active investigation.

Limitations of animal stroke models in drug development

The disparity between successful outcomes after pharmacological intervention in experimental models and failure of clinical trials has been a source of considerable concern in the stroke community.[62] Standards for preclinical studies have been proposed,[63] most notably: benefit confirmed in both rodent and large animal models, involving both transient and permanent arterial occlusions, with appropriate physiological monitoring; replication of results in more than one laboratory; comprehensive dose-response evaluation; and demonstration of a relevant therapeutic window. More recently, concerns regarding data quality assurance have been raised,[64] emphasizing the need for higher standards in experimental design to ensure that studies are adequately powered, properly randomized and blinded, accurately reported, and include appropriate physiological monitoring. At the most fundamental level, future interventional studies in experimental stroke require full awareness of model-specific factors impacting temperature, blood flow, and vascular injury that critically influence outcome. For example, the commonly used intravascular approach to experimental stroke in rodents produces ischemia in widespread regions supplied by the internal carotid artery, including hypothalamus.[65,66] Resultant hypothalamic ischemia gives rise to long-lasting increases in body temperature sufficient to aggravate brain injury and confound pharmacological studies.[65,67–71] Alternative surgical and newer intravascular approaches to selective middle cerebral artery occlusion can avoid such temperature effects.[68,72] An adequate stroke model must also permit sufficiently long occlusions to produce infarcts in cerebral cortex. Less suitable is a model that features rapid striatal injury due to the known selective ischemic vulnerability of neurons in this region,[73,74] as previously established for comparable intervals of transient global ischemia.[7,75] Such injury may not be representative of the focal ischemia in clinical conditions. Another potential confound in transient

intravascular occlusion models is the potential for endothelial damage and a resultant prothrombotic state, with vessel t hrombosis after the filament has been withdrawn resulting in deleterious hemodynamic consequences. This becomes increasingly likely if occluding filaments are polylysine-coated to improve occlusion efficacy.[76] On the other hand such a model may inadvertently better mimic the vascular conditions of a stroke patient with transient arterial thrombotic occlusion. As a related issue, rodent strains differ markedly in the availability of collateral perfusion in brain, profoundly impacting both occlusion susceptibility[24,72,77–80] and intervention efficacy.[24] Comprehensive quantitative regional CBF studies must be performed before a drug's ability to reduce injury can be attributed to a nonhemodynamic neuroprotective mechanism. An improved awareness of model limitations permits their more focused use to address defined experimental questions and better assess therapies targeting specific mechanisms of ischemic injury in brain.

Vascular/Hematologic Pathophysiology and Targets for Therapy

Thrombus formation

Most strokes, whether caused by atherosclerosis or by emboli, involve the process of thrombosis. The heart and the carotid/vertebral extracranial and intracranial arteries represent the most important origins of stroke-related thrombosis. Although the mechanism for thrombus initiation is similar at each of these sites, the rate of clot propagation and its composition have traditionally been thought to differ as a function of the local hemodynamics and other rheologic factors. White thrombi, composed principally of platelets and fibrin, form in areas where blood flow velocity is high and shearing forces near the vascular endothelium are maximum. In areas of low blood flow or blood stasis, such as in the recesses of an enlarged atrial appendage, large numbers of red blood cells are trapped by fibrin to form a red thrombus. Turbulent blood flow with an admixture of high and low velocities favors the formation of thrombi composed of mixtures of platelets, red blood cells, and fibrin.

Thrombi undergo constant change regardless of their initial composition. Proteolytic enzymes from white blood cells, plasma, and the endothelium can remodel the clot and in the process cause embolism, ulceration of an atherothrombotic plaque, or complete clot lysis. Alternatively, the clot may be incorporated into an atherosclerotic plaque and/or continue to enlarge until it occludes the blood vessel lumen.

Recent data[81] have challenged the traditional view of white versus red clot propagation since thromboemboli retrieved from the intracranial middle cerebral and internal carotid arteries in 25 patients with acute ischemic stroke showed similar histologic composition regardless of the vascular or cardiogenic source of the embolus.

Platelets and thrombosis

Arterial thrombus formation occurs almost exclusively at sites of atherosclerosis or injured endothelium.[82] Endothelial damage caused by direct mechanical trauma, hemodynamic stress, infection-inflammation, or immunologic processes exposes collagen of the vessel basal membrane. Collagen, in turn, causes platelets to activate, adhere, and aggregate (Figure **5–2**) to form a nidus from which either a red or white thrombus can evolve. An endothelium-derived protein, von Willebrand factor, binds to glycoprotein Ia/IIa receptors on the platelet surface membrane[83] and fosters the adhesion reaction of platelets to basal membrane collagen. Collagen, circulating epinephrine, thrombin, and a platelet-derived prostaglandin called thromboxane A2 (TXA2) stimulate platelets to release into the circulation the contents of their various cytoplasmic granules.[84] The intensity of this response determines whether the platelets release a few or many substances including adenosine diphosphate (ADP), serotonin, platelet factors 3 and 4, coagulation factor V, fibrinogen, ß-thromboglobulin, and TXA2.

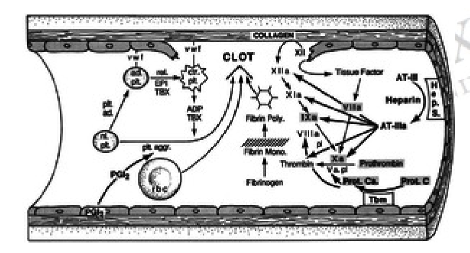


Figure 5–2.
Cutaway view of a blood vessel showing mechanisms of anticoagulation. Heparin activates antithrombin III (AT-III), which inhibits multiple components of the coagulation cascade. Shaded factors represent vitamin-K-dependent proteases and the site of coumadin action. Activated protein C (Prot.Ca) inhibits factors VIII and V. Prostacyclin (PGI2) inhibits platelet activation. Abbreviations: ADP, adenosine diphosphate; ad. plt., adhered platelets; ctr. plt. and c.p.; contracted platelets; EPI, epinephrine; Hep. S, heparan sulfate; mono, monomer; nl. plt., normal platelets; pl, platelet membrane; poly, polymer; Prot. C, protein C; rel., release reaction; rbc, red blood cell; Tbm, thrombomodulin; TXA2, thromboxane A2; Va-XIIa, activated clotting proteases; vwf, von Willebrand factor.

The release-promoting agents, collagen, epinephrine, and TXA2, activate two lipolytic enzymes, phospholipase A2, and phospholipase C in platelet membranes (Figure **5–3**). Activated phospholipase A2 releases arachidonic acid from membrane-bound glycerophospholipids. The enzymes cyclo-oxygenase and thromboxane synthetase then metabolize arachidonic acid to form TXA2.[82] The activation of phospholipase C causes the formation of inositol triphosphate (IP3) that stimulates the release of Ca^{2+} ions from microsomes. Calcium ions in turn trigger myosin phosphorylation and a contraction-secretion process leading to the release of ADP, serotonin, and substances mentioned previously.[85]

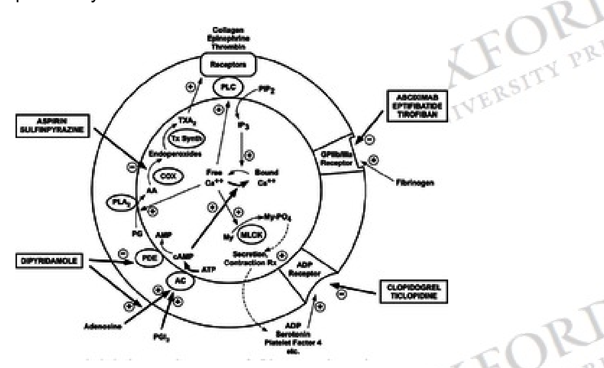


Figure 5–3.
A single platelet showing membrane receptors and cellular enzyme mechanisms of secretion, contraction and aggregation. Fine arrows represent pathways that facilitate platelet aggregation; bold arrows represent pathways inhibiting aggregation. Ovals indicate specific enzymes, and curved arrows an enzyme-catalyzed reaction. Dotted lines identify multistep reaction pathways. Straight lines link a chemical entity with a site of action, at which its effect is either positive (+) or negative (-). Boxes identify therapeutic agents. Platelet aggregation is triggered by collagen, thrombin, or epinephrine interaction with membrane receptors that activate phospholipase C (PLC), leading sequentially to

release of inositol triphosphate (IP3) and calcium, activation of phospholipase A2 (PLA2) and thromboxane A2 (TXA2) production, as well as activation of regulatory cascades leading to contraction and secretion of ADP. Other abbreviations: AA, arachidonic acid; AC, adenylate cyclase; cAMP, cyclic AMP; COX, cyclooxygenase; MLCK, myosin light chain kinase; My, myosin; PDE, phosphodiesterase; PG, phosphoglycerolipids; PGI2, prostacyclin; PIP2, phosphoinositol biphosphate; Tx Synth, thromboxane synthetase.

Platelets, activated via these mechanisms, undergo conformational changes that modify platelet membrane receptor proteins that are critical for aggregation, that is, the cross linking of platelets to form a platelet plug. Preeminent among these platelet membrane receptors for the purpose of aggregation, is glycoprotein IIb/IIIa (GPIIb/IIIa). Glycoprotein IIb/IIIa is a member of the integrin family of membrane proteins and as such is comprised of an alpha and beta subunit.[86,87] Approximately 50 000 to 80 000 GPIIb/IIIa receptors exist on the surface of each platelet with each having specificity or binding sites selective for several proteins, most important among these being fibrinogen.[86,87] The binding of fibrinogen to platelet GPIIb/IIIa receptors serves to bridge one platelet to another thereby creating the three dimensional structural framework that forms the platelet plug. The GPIIb/IIIa receptor protein contains several binding sites that recognize two distinct amino acid sequences, Arg-Gly-Asp (RGD site) and Lys-Gln-Ala-Gly-Asp-Val. Both amino acid sequences are found in fibrinogen and are thought to be involved in the binding of fibrinogen to GPIIb/IIIa.

Coagulation proteins and thrombosis

The coagulation of blood involves a series of proteolytic reactions in which more than 12 coagulation factors (proteases) are activated through an orderly sequence (Figure **5–2**). This proteolytic cascade produces soluble fibrin monomers that polymerize to form insoluble fibrin with cross-links of sufficient strength to stabilize the clot.[88] The sequential nature of the coagulation cascade serves to amplify what may be an initial weak clotting signal; the system also contains multiple control points allowing its fine regulation.

Activation of the intrinsic system, so-called because all components are contained in plasma, occurs when factor XII contacts a nonendothelialized vascular surface with collagen. Activation of factor XII, in turn, activates factors, XI, IX, and with the cooperation of factor VIII, factor X. Factor X represent the crossover point between the intrinsic and extrinsic coagulation systems; the latter being so named because in the test tube, extrinsic tissue thromboplastin is used to initiate coagulation. Both systems participate in thrombus formation. The distinction between the two systems has practical applications in that the most frequently used measures of hemostasis, the partial thromboplastin time (PTT) and the prothrombin time (PT), reflect the activity of the intrinsic and extrinsic systems respectively.[88]

Activation of factor X through either the intrinsic or extrinsic system converts prothrombin to thrombin, which then splits off soluble fibrin monomers from fibrinogen. Through the activation of factor XIII, the soluble fibrin monomers are converted to insoluble fibrin polymers, thereby completing the clotting cascade.

Circulating platelets normally possess little procoagulant activity until they are exposed to collagen. Activation of the platelet-aggregation and release reactions causes several events that lead to platelet procoagulant activity. Con traction of the platelets exposes membrane phospholipids that bind factors V and X, thereby markedly enhancing the rate of prothrombin conversion to thrombin. In addition, platelet phospholipids may enhance the activation of factor X by providing a surface for the reaction of factors VII and IX.[89]

Physiologic antithrombotic mechanisms

Several physiologic processes prevent the active mechanism of platelet aggregation and thrombus formation from creating uncontrolled thrombogenesis. The negatively charged endothelial cells repel like-charged platelets. Rapidly flowing blood clears activated coagulation factors from areas of endothelial injury and the liver removes these activated proteases from the circulation.[82]

Normal endothelial cells suppress platelet aggregation through the synthesis and release of prostacyclin (PGI2), a prostaglandin metabolite of arachidonic acid (Figure **5–4**). Platelet adenylate cyclase activity is enhanced by PGI2 and the accumulation of intracytoplasmic cyclic adenosine monophosphate (cyclic AMP) stimulates the sequestration of free calcium by normal intracellular storage sites and facilitates the inhibition of phospholipase C activity. The latter events act in concert to suppress platelet aggregation.

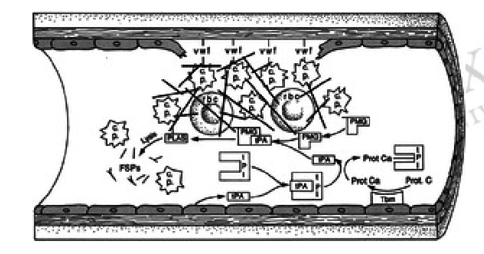


Figure 5–4.
Mechanism of clot lysis by tissue plasminogen activator. Tissue plasminogen activator (tPA) is released from endothelial cells and bound to a circulatory inhibitor protein (tPI). Activated protein C (Prot Ca) releases tPA from inhibitor, enabling tPA to bind to plasminogen (PMG) already attached to the clot. PMG is converted to plasmin (PLAs), which lyses clot into fibrin split products (FSPs). Other abbreviations: c.p., contracted platelets; Tbm, thrombomodulin.

Endothelial cells synthesize two agents with anticoagulant activity. The first, heparan sulfate, is a glycosaminoglycan attached to specific plasma membrane proteins[90,91] on the luminal surface of endothelial cells (Figure **5–2**). In this position, heparan sulfate stimulates the activity of antithrombin III, a circulating protease capable of slowly inhibiting the coagulation factors II, IX, X, XI, and XII. Naturally occurring heparan sulfate or administered heparin markedly enhance the activity of antithrombin III. Thrombomodulin, the second endothelialderived factor with anticoagulant properties, is a receptor lying on the luminal surface of endothelial cells that binds thrombin. Thrombin so bound is unable to split fibrin monomers from fibrinogen. Furthermore, the binding of thrombin to thrombomodulin, in conjunction with factor V, stimulates the activation of protein C. Activated protein C along with a cofactor, protein S, is a potent anticoagulant, which, in the presence of calcium ions and phospholipids, activates factors V and VIII by cleaving their polypeptide chains.[92]

Importantly, activated protein C triggers the fibrinolytic system (Figure **5–4**). The fibrinolytic system is comprised of plasminogen (a 92 kDa serine protease), several plasminogen activators (serine proteases), plasminogen activator inhibitors, and fibrin/fibrinogen. Plasminogen exists in an inactive form until it is cleaved by any of several serine protease activator enzymes, including the endogenous tissue plasminogen activator (t-PA) and urokinase plasminogen activator.[93] Importantly, plasminogen binds to fibrin polymer as the thrombus is formed.[94] Activated protein C binds to and inactivates tissue plasminogen inhibitory protein thereby increasing the concentration of active t-PA.[92] Activated t-PA binds strongly to the plasminogen-fibrin polymer complex within the clot, converting plasminogen into plasmin. Plasmin in turn degrades fibrin polymer into soluble fragments (fibrin degradation products) leading to clot dissolution.

Embolism

Cerebral embolism accounts for about 20% of stroke in the United States.[95] Most emboli originate in the heart, aortic arch, or the carotid arteries supplying the brain.[96] A focal neurological deficit occurs suddenly and maximally at onset and neuroimaging with computerized tomography (CT) or magnetic resonance imaging (MRI) often identifies a peripheral wedge-shaped area of infarction with or without evidence of an occluded vessel. However, it is not always possible on a clinical basis to distinguish cerebral

ischemia arising from embolism, large vessel atherothrombosis, and small-vessel disease, and further testing is required. Even with intensive investigation, embolism often goes unproven, and diagnosis is made on circumstantial evidence. In part, this is because emboli tend to fragment and clear spontaneously more readily than local thrombosis.[97] Angiographic studies of acute stroke have shown that arterial patency to clinically affected areas of brain is 20%–30% at 3–6 hours after stroke onset,[98] spontaneous recanalization increases by another 15%–20% by 8 hours, and arterial patency is 50% by 3 to 4 days after stroke onset.[98–101]

Artery to artery embolism

Platelet aggregates are a common component of artery to artery embolism.[96,102] Red thrombus has been postulated to occur in conditions of blood stasis such as atrial fibrillation. Thrombus may also develop on ulcerated plaques in the carotid bifurcation or as part of an intraplaque rupture. Recent evidence, however, suggests that the histological composition of many emboli may be less distinct than previously believed regardless of whether the source is the heart, aorta, or carotid artery.[81] Embolic material retrieved by an endovascular device from the intracranial internal carotid and middle cerebral arteries showed similar histological features in 75% of 25 consecutive patients with acute stroke, including 16 with a suspected cardiac etiology. These emboli were extracted within 3 to 18 hours of stroke onset and demonstrated random fibrin-platelet deposits interspersed with linear collections of monocytes and neutrophils and confined erythrocyte-rich regions. Red emboli composed exclusively of erythrocytes were uncommon and seen only when embolectomy was incomplete. If a common fibrin-platelet pattern truly dominates the histology of acute embolism, the choice of antiplatelet therapy to treat vasogenic versus anticoagulation to treat cardiogenic emboli may be less important than previously believed.

That emboli can cause transient ischemic attacks (TIA) is well known, but with what frequency is less clear. The rapidity with which an embolus fragments and disperses is one determining factor whether a TIA or stroke ensues.[103] A lower proportion of patients with embolic stroke (40%) have a history of TIA versus those with nonembolic mechanisms (73%).[104] While embolism from a proximal carotid stenosis has been postulated to cause amaurosis fugax and hemispheric TIAs,[105,106] a nonembolic, hemodynamic mechanism cannot be excluded.[107] A small embolus that might occlude retinal arteries might also occlude the tiny pial surface branches of the hemisphere but with little or no symptoms.[108] There is some experimental evidence that tiny emboli can occlude end-arteries in the striatum and elsewhere to produce symptomatic or asymptomatic lacunar strokes.[109–111]

Cardiogenic embolism

The heart is a commonly recognized source for cerebral embolism.[112,113] However, the presence of a cardiac abnormality does not constitute proof ofcardiac embolism. This is especially true if there is extensive systemic atherosclerosis or if the significance of the cardiac lesion is not clear.[114] Cardiac disorders associated with embolism include atrial fibrillation (especially with mitral stenosis), infectious and noninfectious endocarditis, acute myocardial infarction, congestive heart failure, and other cardiomyopathies characterized by severe ventricular dysfunction. Cerebral embolism can also complicate cardiac catheterization, open-heart surgery, and cardiac transplantation.[115,116]

Atherosclerosis

Atherosclerosis commonly affects the aorta, the extracranial portions of the internal carotid and vertebral arteries and the intracranial vessels. Atherosclerosis affects primarily large and medium-sized arteries but it can also affect small arteries and arterioles. The disorder starts when the arterial endothelium is injured by high levels of blood cholesterol, toxins from cigarette smoke, elevated blood glucose, hypertension, or some combination of these risk factors. Once the atherosclerotic lesion forms, it gradually grows at the site of injury to produce a plaque consisting of cholesterol, calcium, cell debris, platelets, and connective tissue. This plaque can rupture to release embolic debris (e.g., aorta) or trigger thrombus formation with secondary embolism. The plaque can gradually increase in size until it occludes the arterial channel. While blood flow is typically increased at the point of stenosis, post-stenotic blood flow may be reduced in velocity. This can result in a hemodynamic stroke if blood pressure falls for any reason or the stagnant blood flow can clot spontaneously, completely blocking the channel.

Lipohyalinosis, microatheroma, and lacunar infarcts

In the 1960s, the concept of lacunar stroke was refined by C. Miller Fisher who performed a meticulous histological analysis of 68 lacunar infarcts in 18 brains.[117–121] Lacunes consisted of small, deep cerebral infarcts following occlusion of a single perforating artery. Arterial hypertension and intracranial atherosclerosis were the major risk factors in their pathogenesis. For the smallest lacunes, Fisher described a segmental arterial pathology affecting the penetrating arteries 40 to 200 μm in diameter and coined the term *lipohyalinosis*. In the acute phase, lipohyalinosis was characterized by fibrinoid necrosis. Later stages demonstrated loss of normal architecture in the vascular wall, collagenous sclerosis, and lipid-laden macrophages. Because of their small size, many of these lacunes were asymptomatic and required no further treatment than control of risk factors and perhaps aspirin. However, he also studied larger lacunes, and here he found microatheroma at the origin of penetrating arteries 200 to 800 μm in diameter. Some of these had a local thrombus. Due to the larger size, these lacunes were more likely to be symptomatic, and depending on their location in the brain, the lacunar infarcts produced a spectrum of lacunar syndromes often with highly selective deficits such as pure motor hemiparesis. Because some lacunes contained thrombus, they became regarded like any other infarct in which atherothrombosis played a role.

However, the pathophysiology of lacunar infarction has not been without controversy. Lacunar infarcts are more frequent in the presence of severe carotid plaques suggesting a hemodynamic influence in their generation[122,123] and in diabetics.[124] Furthermore, data exist that emboli can produce small infarcts indistinguishable from lacunes.[110,111,125] A revisionist analysis of Fisher's own data suggests that pathologies other than lipohyalinosis are not uncommon and that “there is no longer a specific vascular occlusive pathology of little strokes.”[126(P903)] Similarly, the distribution of stroke risk factors for lacunar infarcts may well be no different from that found for nonlacunar stroke.[109] It is notable that small vessel occlusive strokes benefited the most from acute thrombolysis with recombinant tissue plasminogen activator, rt-PA.[127] The upshot is that the term *lacunar* stroke has lost its special pathophysiologic meaning and now simply means a small stroke. Therefore, it needs investigation for underlying etiologies just like the large strokes.

Other arteriopathies

There exist a number of cerebral arteriopathies that predispose to stroke.[128] Detailed discussion of these is beyond the scope of this chapter. One major category involves noninflammatory arteriopathies: cervical dissection, fibromuscular dysplasia, vasospasm in subarachnoid hemorrhage, Moyamoya, migraine-associated stroke, and drug induced (amphetamines and cocaine). In this group are certain inherited arteriopathies associated with stroke including Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), Fabry disease, sickle cell disease, and homocystinuria. The other major category features vascular inflammation and includes: systemic vasculitis due to polyarteritis nodosa, Churg-Strauss angiitis, systemic lupus erythematosus, Wegener's granulomatosis, rheumatoid arthritis, and giant cell angiitis. Infectious etiologies include syphilis, bacterial, fungal, rickettsia, varicella zoster, and HIV. Isolated angiitis of the central nervous system (CNS) is very rare.

Drugs and their mechanisms of action

Thrombolytic Agents

Tissue-type plasminogen activators

Naturally occurring tissue plasminogen activator (t-PA) is a glycosylated serine protease comprised of 527 amino acids and ~70 kDa molecular weight. Four identifiable domains with distinct properties are contained within the molecule. The 47 residue amino terminal end of the molecule harbors the fibrin binding region and is homologous to other protein finger domains. A 38 amino acid residue shares homology with human epidermal growth factor. Two regions, comprised of 38 (krinkle 1) and 90 (krinkle 2) amino acid residues respectively, share homology with the krinkle regions of plasminogen. The 252 residue carboxy terminal end of the molecule contains the serine protease, the active site for plasminogen cleavage to plasmin.[129]

Vascular endothelial cells throughout the body produce t-PA but it is also synthesized by CNS neurons and astroglia. In addition to its ability to cleave and activate plasminogen to plasmin, t-PA may also participate in CNS vascular permeability, vascular remodeling, brain cell migration, and CNS development.[130,131] Of greater concern are reports of t-PA facilitating excitotoxic mechanism leading to neurodegeneration[132] and increasing cerebral infarction volume from focal brain ischemia in rodents.[133]

Alteplase (Activase) is a single chain 68 kDa molecule, recombinant tissue-type plasminogen activator (rt-PA) produced by inserting complimentary DNA (cDNA) to human t-PA obtained from human melanoma cells into Chinese Hamster Ovary cells for large scale expression. Injected into the circulation, Alteplase is rapidly cleared by the liver with an initial half-life of approximately five minutes.[134] Alteplase activation of plasminogen, like that of endogenous t-PA, is heavily fibrin-dependent because of its relatively weak binding to fibrinogen but strong binding to fibrin and especially to fibrin-bound plasminogen.[129]

Alteplase is administered intravenously to patients with acute ischemic stroke only after careful evaluation following the inclusion/exclusion guidelines reported by the Stroke Council of the American Heart/Stroke Association.[135] Treatment must be initiated within three hours of symptom onset and treatment with alteplase is not recommended for patients with minor or rapidly improving neurologic symtoms. The dose of alteplase is 0.9 mg/kg, not to exceed 90 mg total dose, infused intravenously over 60 minutes with 10% of the total dose given as a bolus infusion during the initial first minute. Anticoagulants and antiplatelet agents should be held for 24 hours after the infusion. The most common adverse reaction of all forms of thrombolytic therapy in acute ischemic stroke patients is intracerebral hemorrhage (ICH). In the most frequently referenced National Institute of Neurological Disorders and Stroke (NINDS) t-PA Stroke Trial[127] symptomatic intracerebral hemorrhage occurred in 6% of the alteplase treated population versus less than 1% in the control group.

Reteplase (Retavase) is a nonglycosylated, 39 kDa deletion-mutant protein of naturally occurring t-PA that has been genetically engineered to lack the finger, epidermal growth factor, and krinkle 1 domains of t-PA. Loss of the finger or fibrin binding domain leads to lower fibrin binding, slower hepatocyte clearance, and a longer biologic half-life of approximately 14 minutes compared to t-PA.[134] Theoretically, these engineered properties should permit bolus injection in place of continuous infusion and the lower fibrin binding should decrease peripheral fibrinolysis and systemic hemorrhagic complications. Safety and efficacy in acute ischemic stroke are the subject of several clinical trials.

Tenecteplase (TNKase) is a genetically engineered 65 kDa mutant protein of naturally occurring t-PA with three amino acid substitutions. The resulting molecule has a longer halflife of approximately 15 minutes, higher fibrin specificity, and increased resistance to plasminogen activator inhibitor protein compared to naturally occurring t-PA.[134] Tenecteplase was tested in a Phase I, dose-escalation safety trial for patients with ischemic stroke[136] but its efficacy in this population remains to be determined.

Desmoteplase is a recombinantly manufactured form of the α-1 variant (DSPAα-1) of naturally occurring plasminogen activators found in the saliva of vampire bats *(Desmodus rotundus)*. DSPAα-1 is a single chain protease with ~70% amino acid homology with human t-PA.[137] Importantly, the proteolytic activity of DSPAα-1 is increased in the presence of fibrin almost 200 fold greater than that of t-PA[138] and DSPAα-1 is associated with a lower level of systemic circulatory fibrinolysis than t-PA.[139] Promising results from Phase II testing in human stroke[140] led to a Phase III trial of DSPAα-1 that proved disappointing in a preliminary report presented in 2007 prior to publication.

Urokinase chemistry is complicated by the existence of several forms of the active molecule. Glycosylated, single-chain, high molecular weight (54 kDa) urokinase (hmwscu-PA) is secreted by kidney cells and may be isolated from urine.[94] Low molecular weight (32 kDa), single chain urokinase (lmwscu-PA) is made by and isolated from cultures of human neonatal kidney cells.[94] Both forms activate plasminogen to plasmin and both forms have been adapted for pharmacologic use. A recombinant form of the hmwscu-PA developed and produced from a murine hybridomas cell line was named Prolyse, also known as pro-urokinase (rp-UK), and the lmwscu-PA form for pharmacological use was named Abbokinase. Despite positive results reported for several clinical trials of the high molecular weight urokinase or rp-UK (Prolyse) in myocardial ischemia[141] and stroke,[142] Prolyse was removed from the market in 1999 because of manufacturing problems and has not been reintroduced.[143] Prolyse was administered intra-arterially to patients with occluded middle cerebral arteries in the Prolyse in Acute Cerebral Thromboembolism Trial II (PROACT II)[144] but despite positive results it was not approved for this use by the U.S. Food and Drug Administration (FDA).

Ancrod (Arwin, Viprinex) is a glycosylated serine protease of 234 amino acid residues and 35 kDa molecular weight produced in the venom of a variety of poisonous snakes. Ancrod (Viprinex) is purified from the venom of the Malaysian pit viper (*Calloselasma Rhodostoma*) because of its high concentration in this snake's venom.[145] Ancrod produces rapid defibrinogenation of blood by cleaving fibrinopeptides FpA, FpAP, and FpAY from the A-alpha chain of fibrinogen.[146] The cleavage of these peptides from fibrinogen produces fibrin monomers similar to those produced by thrombin activity on fibrinogen with the important distinction that ancrod fibrin monomers are incapable of cross linkage.[146] Ancrod has no direct effect on blood coagulation factors nor does it directly activate plasminogen.[147] However, the depletion of circulating fibrinogen removes the critical substrate for thrombus formation and the fibrin breakdown products stimulate endogenous plasminogen activators.[148] Thus ancrod functions as both an anticoagulant and a plasminogen activator albeit through indirect mechanisms. Since blood coagulation factors are left undisturbed by ancrod, measured doses of ancrod tend to have lower bleeding complications than typical anticoagulants.[148] Ancrod has a half-life of 3–5 hours and is administered intravenously via infusion. Blood fibrinogen levels are monitored and the rate of ancrod infusion is adjusted accordingly.

Antiplatelet Agents

Cyclo-oxygenase inhibitors

Aspirin (acetylsalicylic acid), is well absorbed in the stomach and small intestine within 4 to 10 minutes of oral administration reaching peak plasma levels by 30 to 40 minutes.[149] In contrast, enteric-coated aspirin may require up to 3 to 4 hours to reach peak plasma levels. Aspirin is hydrolyzed in the liver producing salicylic acid, an inactive metabolite excreted by the kidney. The plasma half-life of aspirin is 15 to 20 minutes. Although usually well tolerated, aspirin prolongs the bleeding time and may cause gastric erosion and gastrointestinal bleeding.

At cumulative daily doses of less than 30 mg, aspirin acts by irreversibly acetylating platelet cyclo-oxygenase, thereby blocking thromboxane (TXA2) synthesis (Figure **5–3**).[149,150] The loss of TXA2 decreases platelet phospholipase C and increases adenylate cyclase activities. The resulting fall in platelet inositol triphosphate and diacylglycerol levels, plus the enhanced platelet cyclic AMP levels, lead to inhibition of platelet aggregation. At higher daily doses (>40 mg) aspirin transiently inhibits endothelial cell cyclo-oxygenase, and the salicylate moiety inhibits endothelial cell lipoxygenase as well, both effects that can lessen the beneficial effect of TXA2 suppression.[149] These considerations weigh in favor of low dose aspirin for long term prophylaxis but the pharmacokinetics of aspirin absorption, metabolism, and its effects on platelet acetylation dictate that higher doses (~200 mg) of nonenteric-coated aspirin be given in the setting of acute stroke. After several days the dose may be reduced to ~50 to 75 mg daily.[149]

Platelet glycoprotein iib/iiia receptor blockers

All of the GPIIb/IIIa receptor blockers currently remain experimental therapies for acute ischemic stroke, are not FDA approved for this indication, and should be used to treat acute ischemic stroke only under carefully planned and Internal Review Board (IRB) approved clinical protocols with patient informed consent.

Abciximab (ReoPro) is a murine monoclonal antibody directed against the GPIIb/IIIa receptor in which the Fc fragment (73E) of the antibody was removed before joining the remaining Fab fragments with the constant regions of human immunoglobulin to create a human-murine chimeric antibody.[87] Abciximab binds to the GPIIb/IIIa receptor and blocks the binding of fibrinogen, Von Willebrand factor, and other adhesive molecules to this receptor site thereby inhibiting platelet aggregation. Greater than 80% blockade of the GPIIb/IIIa receptor can be achieved in humans with a single bolus intravenous injection of 0.25 mg/kg followed by a continuous maximum infusion rate of 10 μg/min for 12 to 96 hours.[151] A dose regimen very similar to this was tested in patients who experienced an ischemic stroke within 56 hours of symptom onset (AbBEST II Trial) but unfortunately the study was discontinued prior to completion because of a high incidence of intracranial hemorrhage.

Eptifibatide (Integrilin) is a cyclic heptapeptide containing a lysine-glycine-aspartate sequence that is thought to interact with specific binding sites on GPIIb/IIIa. The plasma half-life of eptifibatide is approximately 2.5 hours.[152] Eptifibatide is a reversible inhibitor of fibrinogen binding and requires continuous infusion to maintain adequate inhibition of platelet aggregation. Eptifibatide is currently undergoing testing in patients with acute ischemic stroke in conjunction with the administration of intravenous rt-PA.

Anticoagulants

Heparin is a proteoglycan comprised of a heterogeneous group of mucopolysaccharides composed of repeating disaccharide units of different lengths. Commercial heparin is extracted from either bovine lung or porcine intestinal mucosa. Heparin markedly accelerates the binding of circulating antithrombin III to activated coagulation factors II (prothrombin), IX, X, XI, and XII with the predominant effect on factor X (Figure **5–2**). The binding of antithrombin III to the activated coagulation factors irreversibly inhibits their procoagulant activity.[90,91] Heparin produces immediate anticoagulation with a dose-dependent half-life ranging up to 5 hours.

Heparin is poorly absorbed from the gastrointestinal tract, and must be administered either by deep injection in body fat or intravenously. Continuous intravenous infusion is the method of choice for administering heparin to patients with acute ischemic stroke. Depending on the urgency of achieving the anticoagulated state, an initial bolus of 5000 U may or may not be administered prior to continuous infusion adjusted to a level that will maintain the activated PTT in the range of 1.5 to 2.0 times the patient's pre-heparin control PTT.

The principal complication of heparin therapy is hemorrhage. In addition, heparin administration for one week or longer can produce thrombocytopenia in as many as 5% of patients, either by increasing platelet aggregation or by inducing antiplatelet antibodies. The latter condition is more frequently encountered with heparin derived from bovine lungs than from porcine intestines.[153] Paradoxically, heparin may promote coagulation by reducing antithrombin III levels and also by stimulation of platelet aggregation.

Enoxaparin (Lovenox) is low molecular weight heparin isolated from porcine intestinal mucosa heparin with an average molecular weight of approximately 4.5 kDa. Importantly, heparin molecules of this size do not accelerate the binding of antithrombin III to prothrombin and consequently enoxaparin has little measurable effect on the partial thromboplastin time (PTT). Enoxaparin does accelerate the binding of antithrombin III to coagulation factor X and thereby produces an anticoagulant effect.[153] Enoxaparin is administered by subcutaneous injection in a dose of 40 mg daily to prevent deep venous thrombosis and pulmonary embolism in stroke patients. Enoxaparin can produce thrombocytopenia with a similar frequency and severity to that of unfractionated heparin.

Neuroprotectants

Albumin has recently undergone a successful pilot trial (Albumin in Acute Stroke, ALIAS) that found the agent to be well tolerated at targeted therapeutic doses of up to 2 g/kg,[154] the only recognized adverse effect being a predictable increase in the risk of pulmonary edema that could be managed with diuretics.

Although considered here in the context of neuro-protectant strategies, the mechanisms of albumin action remain to be defined and the preclinical data in balance favor an intravascular site of action. Early studies undertaken to examine benefits of hemodilution in experimental stroke were equivocal, but beneficial effects of albumin infusion in experimental stroke were occasionally noted.[155,156] A surge in interest began with the demonstration of significant protection with bolus albumin infusion initiated at the time of reperfusion following transient focal ischemia,[157,158] showing reductions in infarct volume, edema, and vascular injury, with subsequent demonstration of a therapeutic window of up to four hours.[159] Less pronounced, but significant, benefit was also seen in a model of permanent occlusion.[160] Albumin treatment was associated with improved CBF following release of occlusion,[161] an effect that was perhaps more evident when infused during permanent occlusions.[160] Further studies demonstrated reduced leukocyte adhesion, improved microvascular patency, and increased capillary flow velocities after albumin treatment during postischemic recirculation.[162] It is important to note that all of these studies involved a particular focal ischemia model in which a polylysine coated filament was inserted into the internal carotid artery of Sprague-Dawley rats.[76] By facilitating occlusion efficacy in a strain that otherwise possesses robust collateral perfusion,[24,72] this produces a large penumbra of potentially salvageable tissue, and the procedure almost certainly results in a residual prothrombotic state within the vasculature that would sensitize it to interventions that improve microvascular perfusion. Since the latter condition may also characterize the brain vasculature following clinical ischemia/reperfusion, this may have provided a particularly robust model in which to identify an agent with such effects. Albumin was also found protective in models of traumatic brain damage[163] and hematoma,[164] which may include components of vascular injury.

Albumin is a complex molecule[165] and even at the microvascular level its mechanisms of action remain uncertain. The initial report of its clinical efficacy cites a range of potential effects that would beneficially impact microcirculation after stroke,[166] including reduced platelet aggregation, vasodilation, and direct antiadhesive effects, and there remains the potential impact of hemodilution per se. It has recently been speculated that exogenous albumin could provide an additional sink for lysophosphatidylcholine (lyso PC),[167] which might otherwise trigger endothelin-1-mediated vasoconstriction. Human albumin and its species-specific N-terminal tetrapeptide also exhibit antioxidant effects, likely due to their metal binding capacities.[168]

NXY-059 (disodium 4-[(tert-butyl imino) methyl]benzene-1,3,-disulfonate N-oxide) is a water-soluble spin trapping agent based on aphenyl-N-tert-butyl nitrone (PBN). This was a promising drug for stroke treatment on theoretical grounds, designed to target several radical species that are produced during ischemia/ reperfusion and believed to contribute to reperfusion injury. The compound appeared to have satisfied the Stroke Therapy Academic Industry Roundtable (STAIR) criteria for preclinical trials,[63] having demonstrated efficacy in rodent[169–171] as well as primate stroke models,[172,173] with a long therapeutic window, and some evidence to indicate brain entry.[174] The drug was well tolerated in patients.[175,176] An initial double-blind study suggested detectable clinical benefit,[177,178] although the analysis was immediately questioned,[179] and a subsequent negative trial halted further development.[180]

This latest failure for a neuroprotectant deserves a brief evaluation of the experimental studies that provided the optimistic foundation for the clinical trials. The dose-dependence of protection varied considerably in rodent studies.[71,169–171] However, almost complete elimination of infarction was reported at high doses in one permanent occlusion study,[170] which would be difficult to explain without invoking increased blood flow. In view of evidence suggesting perfusion effects of the parent compound, PBN,[181] it is surprising that there was no comprehensive evaluation of CBF following NXY-059 administration.[182]

Primate studies demonstrated marked neurological benefit and infarct reduction at a long survival interval when NXY-059 was administered immediately after occlusion,[173] with some histological protection remaining at a four-hour treatment window.[172] Although this involved verifiably successful surgical middle cerebral artery (MCA) occlusion, the model itself is not well characterized with respect to the distribution and magnitude of the CBF deficits produced. There was evidence of protection with early treatment in small-embolus but not largeembolus stroke models,[183,184] the latter showing somewhat paradoxical effects to increase hemorrhage when administered alone, but reduce hemorrhage after treatment with t-PA. NXY-059 treatment reduced behavioral deficits in a rat hemorrhagic stroke model and acutely attenuated neutrophil infiltration, with no long term effects on the histological lesion.[185] As a final point, unequivocal brain entry of the drug was not demonstrated,[171,174,186] leading to suggestions that vascular sites of action may have been involved in any observed effects.[182,187]

Gavestinel (GV150526) is a substituted indole-2-carboxylate with a highly selective affinity for the glycine site of the N-methyl-D-aspartate (NMDA) receptor.[188,189] At this site, gavestinel has no agonist activity but antagonizes effects associated with the activation of the NMDA receptor. In experimental models of excitotoxicity and ischemic stroke, gavestinel has produced neuroprotection comparable to other NMDA antagonists. In one rodent study, however, gavestinel appeared to reduce infarct size by 50% when given up to six hours after occlusion of the middle cerebral artery.[190] This high degree of protection was not observed with other drugs. Unlike other NMDA antagonists, gavestinel does not cause neuronal vacuolization, impair learning or induce phencyclidine-like behavior.[191] In a phase II safety study, 48 patients tolerated the drug without any hemodynamic or CNS adverse effects when compared to 18 placebo controls.[192] Three patients showed a transient, asymptomatic rise in liver enzymes that never exceeded twice normal levels and therefore was considered trivial. This encouraging profile for the drug prompted two large multicentered phase III studies in North America (GAIN Americas) and in Europe (GAIN International) that were run in parallel. The drug was administered within six hours of ischemic stroke onset and the patient's functional outcome three months later was measured by the Barthel Index. In both studies, gavestinel failed to improve outcome.[193,194] The yet another failure of a promising neuroprotective agent produced considerable introspection and commentary in the stroke research community as to why the drug failed. Mortality and adverse events were similar in treated patients and controls. Importantly, the preclinical testing failed to meet the standards put forth by STAIR and published in 1999 in the journal *Stroke* after the GAIN trials had begun. For example, infarct reduction with drug administered six hours after MCA occlusion was never reproduced in an independent laboratory and published in a peer-reviewed journal. The consistent failure of multiple glutamate antagonists to attenuate ischemic stroke has even led some investigators to question the role of glutamate excitotoxicity in the evolution of ischemic damage.[41]

Repinotan (BAYx3702) is a highly selective serotonin (5-HT1A) receptor agonist that has shown neuroprotective effects in animal models of middle cerebral occlusion with the drug administered as late as five hours after occlusion.[195] Repinotan produced impressive, dose-dependent infarct reductions following permanent and transient middle cerebral artery occlusion in rats. The mechanism of neuroprotection is conjectured to involve neuronal hyperpolarization when the drug binds to 5 HT1A receptors with consequent inhibition of neuronal firing and suppression of glutamate release.[196] Phase II studies showed the drug to be safe with headache as the most common side effect.[197] The dose and time-dependent neuroprotective efficacy of the drug appeared promising for use in human trials. Unfortunately, the first, randomized, double-blind, placebocontrolled clinical trial failed to show any benefit of the drug when given within 4.5 hours of ischemic stroke,[198] and with that negative outcome, Bayer ended the development of Repinotan for stroke treatment.

Piclozotan (SUN N4057) is a (5-HT)1A receptor agonist with pronounced neuroprotection in animal models of middle cerebral artery occlusion. In 2004, a phase II study was initiated to determine if a 72-hour infusion of piclozotan started within six to nine hours of acute ischemic stroke onset could salvage ischemic penumbra as defined by MRI (perfusion-weighted imaging minus diffusion-weighted imaging volume). The study plans to recruit 112 patients with focal cortical signs and a moderate-to-severe neurological deficit National Institutes of Health Stroke Scale (NIHSS score of 6–22). Patients will receive study drug or placebo at less than six hours after stroke onset (50% of subjects) or between six and nine hours after onset. Infarct volumes measured by MRI will be compared in each group at one month and clinical outcomes assessed at one and three months.[199]

Citicoline stimulates the synthesis of phospholipids for the neuronal membrane and may have anti-apoptotic and neuroplasticity effects in ischemic stroke. A phase III trial showed no difference between citicoline and placebo in the percent of patients with greater than seven points improvement on the NIH stroke scale at three months after stroke.[200] Another international phase III trial with similar aims, the ICTUS study, is still ongoing.

DP-b99 is a membrane-activated metal ion chelator that showed neuroprotection in preclinical studies. Phase I and II trials have shown that DP-b99 is safe in stroke patients with no major adverse effects.[201] A Phase IIb trial commenced in 2005 to confirm the safety and test the efficacy of this compound. Patients presenting within six to nine hours of stroke onset receive the medication intravenously over four days. Primary outcome is change in the NIHSS score at three months.

Zonampanel blocks the action of glutamate as an AMPA receptor antagonist.[199] A large multicenter, double-blind, placebo-controlled, randomized trial (ARTIST) is testing the drug as an add-on to t-PA given within three hours of onset. Efficacy will be determined by neurological and functional scales. A companion trial (ARTIST MRI) will examine patients with stroke onset less than six hours and who show salvageable ischemic penumbra as defined on MRI by a diffusion-perfusion mismatch of 120% or greater. Primary outcome is infarct volume measured by MRI at three months.

Acute management of ischemic stroke

General Considerations

Definition of ischemic stroke and tia

Since 1995, important advances in neuroimaging have become widely available (e.g., MR diffusion weighted imaging and CT-angiography) and thrombolytic therapy for acute stroke has become established as standard of care. This has revolutionized the clinical approach to stroke by improving diagnostic accuracy, by recognizing the urgency to restore the cerebral circulation and by choosing therapies that are increasingly grounded in pathophysiological considerations.

The typical ischemic stroke involves the appearance of sudden, focal neurological deficits that last at least 24 hours[202] and arise from an acute occlusion of an artery supplying the brain. Deficits lasting less than 24 hours were until recently labeled as TIA because permanent brain injury was believed not to have occurred. MR diffusion-weighted imaging (DWI), however, has detected increasing cerebral damage when symptoms of ischemia persist beyond one hour.[203] That information has led to a new definition for TIA, namely, that symptoms must resolve within one hour.[204,205] Conversely, the temporal spectrum of ischemic stroke has been expanded to include instances in which symptoms resolve within 24 hours but the DWI shows permanent (subclinical) ischemic damage.

Classification of ischemic stroke

In the highly charged setting when thrombolytic therapy is being considered for a hyperacute stroke, it is not usually possible to identify the pathogenetic mechanism of stroke with precision. Nonetheless, the history, exam, and neuroimaging permit most strokes to be grouped rapidly into one of three major categories: large vessel occlusion (atherothrombosis), cardiac embolism, and small vessel occlusion (lacunar stroke). How each category of stroke should be managed to restore cerebral perfusion and to limit ischemic injury is controversial and under active investigation.

Large vessel occlusion (atherothrombotic stroke)

When a cardiac source cannot be clearly identified, atherosclerosis typically underlies the pathogenesis of acute stroke due to large vessel occlusion. In both extracranial and intracranial arteries, atherosclerotic plaques gradually enlarge to compromise the arterial lumen. The intracranial vasculature is affected more in African Americans and Asians, whereas whites have more extracranial disease (i.e., stenosis of the carotid bifurcation). Stenotic arteries can lead to reduced cerebral perfusion when blood pressure drops for whatever reason (e.g., cardiac arrhythmia) and produce either a hemodynamic TIA or a so-called water-shed infarction if the perfusion pressure is not quickly restored. Such plumbing problems can be quickly addressed with arterial stenting or endarterectomy. More often, however, gradual arterial stenosis leads to local thrombosis and complete occlusion of the artery with or without a distal propagation of the clot. Because of collateral flow across the circle of Willis, complete occlusion of the internal carotid may be asymptomatic until the clot breaks off and embolizes distally to occlude the middle cerebral artery; alternatively, plaque fragments may embolize distally and also produce artery-to-artery embolism. Because it is sometimes very difficult to know if intracranial arterial occlusion is due to local thrombosis at the site of an atheromatous plaque or due to embolism from a proximal source, the term *thromboembolism* is sometimes used to cover both possibilities. In this category, the aorta is an often overlooked as a potential source of embolism because transesophageal echocardiography is often omitted. The occurrence of amaurosis fugax as a TIA is more likely in atherothrombotic stroke than in other types of stroke and serves as a clue to exclude the other two categories.[205] Otherwise, stroke due to large vessel occlusion from atherothrombosis is diagnosed when the neurological exam localizes the lesion to a specific large arterial territory, neuroimaging (e.g., DWI, magnetic resonance angiography [MRA], CT-angiography [CTA]) confirms the site of the lesion and there is no evidence for a cardiac source of embolism.

Cardioembolic stroke

Cardioembolism is diagnosed when a cardiac source of emboli is identified (e.g., valvular vegetations on echo) and no other obvious cause for stroke is apparent (e.g., arterial imaging shows little disease except at the point of embolic occlusion). Common risk factors for cardioembolic stroke include atrial fibrillation (especially if unstable and recurrent), atrial flutter, valvular disease (e.g., endocarditis, mechanical valves), left to right shunt (e.g., patent foramen ovale with septal aneurysm), recent myocardial infarction, and left ventricular hypokinesis (i.e., ejection fraction <30%).[205,206]

Small vessel (lacunar) stroke

The third major category of acute stroke involves the occlusion of the small, penetrating arteries that supply the deep white matter (e.g., centrum semiovale), deep gray matter of the cerebral hemispheres (e.g., basal ganglia, thalamus), and the brainstem (e.g., pons). These arteries have poor collateral supplies and many can be considered end-arteries. Microatheroma are believed to underlie the pathogenesis of most of these lesions. Depending on the site of the lesion, the clinical presentation may be silent or may

produce one of the so-called lacunar syndromes, such as pure motor hemiparesis, pure sensory hemianesthesia, ataxic-hemiparesis, dysarthria-clumsy hand, and others.[118] MRI is more sensitive than CT in detecting these small infarcts, especially in the posterior fossa. Prognosis is typically good for recovery of neurological function but in the context of labile hypertension, multiple subclinical lacunar strokes may lead to vascular Parkinsonism and/ or subcortical dementia (Binswangers disease).

Stroke code and early recognition of stroke

Stroke Code refers to a system that permits the rapid identification, prenotification and transport of acute stroke patients to a specialized stroke center.[207] The community is educated to recognize stroke symptoms and is encouraged to call 911 promptly. Early stroke recognition is vital if intravenous rt-PA is to be used within three hours of stroke onset as approved by the FDA.[127] “Time is brain” is a slogan that emphasizes any delay in treatment results in brain loss. The landmark 1995 NINDS rt-PA clinical trial developed a prototype approach to acute stroke that required close cooperation between members of emergency medical systems (EMS), emergency departments (ED), radiology, neurology, and hospital administration. Their model formed the basis for the stroke code and is not unlike acute care protocols developed for trauma patients and myocardial infarction. When EMS recognizes a potential stroke, the local ED is alerted and the stroke team is immediately notified by page. The stroke team should arrive no later than 15 minutes of being called (Table 5–1).[208] The goals of the initial evaluation are to confirm that the patient’s neurological deficits are due to ischemic stroke, assess the reversibility of the pathology based on the time of onset of stroke, obtain clues to the mechanism and etiology of stroke, and determine if there are any contraindications for thrombolytic therapy (or thrombolectomy in select centers). Time guidelines for managing an acute ischemic stroke have been proposed by a consensus panel convened by the NINDS (Table 5–1).[135,208]

Table 5–1 NINDS Recommended Time Guidelines for Acute Ischemic Stroke Management

Time from ED Arrival to Task Completion	
ABCs, cardiac monitor, IV access, blood sugar Alert ED with acute stroke care capability (if patient is brought by EMS)	−10 min
ED neurological screen, ABCs, IV access, blood samples, call stroke team, order STAT head CT, 12 lead EKG	10 min
Stroke team or designee, determine time of stroke onset, NIH Stroke Scale	25 min
CT excludes hemorrhage, check for fibronolytic exclusions, check if deficits are rapidly improving	45 min
Review risks/benefits of tPA with patient and family. Start tPA	60 min
ICU monitor, no anticoagulants or antiplatelets for 24 hours	

Vascular Recanalization and Cerebral Reperfusion

Thrombolysis

Rapid lysis and dispersal of an arterial thromboembolus can restore cerebral blood flow, limit brain injury, and improve outcome in ischemic stroke. Currently, intravenous recombinant tissue plasminogen activator (alteplase) is the only thrombolytic drug approved by the FDA for use in acute stroke. One other thrombolytic agent, recombinant pro-urokinase (rp-UK) or Prolyse, demonstrated efficacy in opening the MCA when given intra-arterially within six hours of stroke onset. It did not, however, receive approval from the FDA due to a high rate of thrombolysis-related intracranial hemorrhage. Interventional radiologists nonetheless use intra-arterial alteplase or urokinase off label to dissolve clots and restore vessel patency between three and six hours after stroke onset.

Intravenous thrombolysis

Alteplase (Activase). The FDA gave its approval for using intravenous rt-PA to treat ischemic stroke within three hours of symptom onset based on the NINDS rt-PA trial reported in 1995. The trial compared intravenous rt-PA (0.9 mg/kg) to placebo in subjects that met specific inclusion-exclusion criteria (Table 5–2). After 10% of the total dose was infused as a bolus, the remaining rt-PA was administered over one hour. Three months later, neurological outcome was more favorable in rt-PA treated patients. Roughly 12% more patients had minimal or no neurological disability when compared to the placebo group. Even though rt-PA patients suffered more symptomatic intracerebral bleeds than controls (6.4% versus <1%) including 3% fatal hemorrhages, mortality was similar between rt-PA-treated and placebo-treated patients. Fewer deaths due to ischemic stroke in the rt-PA group offset the deaths due to brain hemorrhage. Nonetheless, rt-PA is potentially dangerous and any departure from current guidelines[135] may tilt the risk-benefit ratio toward greater harm. Furthermore, the risks of using rt-PA versus withholding rt-PA should always be explained to patient and family before treatment.

Table 5–2 Inclusion and Exclusion Criteria for Intravenous rt-PA for Acute Ischemic Stroke
Inclusion criteria Age >18 y Clinical diagnosis of ischemic stroke with a clearly defined time of onset of <3 h Neurological deficit measurable on the NIH Stroke Scale Treating major deficits requires special caution Risks and benefits of thrombolysis understood by patient or family
Exclusion criteria CT of the brain shows intracranial hemorrhage or multilobar infarction (hydrossity > 1/3 of cerebral hemisphere Rapidly improving or minor symptoms Systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg Aggressive treatment required to reduce blood pressure to the specified limits Use of anticoagulants with INR > 1.7 Use of heparin within the previous 48 h and elevated partial thromboplastin time Platelet count <100 000 mm^3 Blood glucose <50 mg/dL (2.7 mmol/L) or >400 mg/dL (22.2 mmol/L) Another stroke, myocardial infarction or serious head trauma within the preceding 3 months Major surgery within the previous 14 d History of intracranial hemorrhage Symptoms suggestive of subarachnoid hemorrhage Gastrointestinal or urinary tract hemorrhage within the previous 21 d Arterial puncture at a noncompressible site within the previous 7 d Active bleeding or acute trauma (fracture on exam) Seizure with residual postictal neurological deficits

In the years since the NINDS rt-PA trial was published, its investigators have further analyzed the data and issued several elaborations to their conclusions that impact recommendations for rt-PA use.[135,209,210] First, exclusion of patients based on ischemic stroke type, advanced age, or stroke severity was not supported by their post hoc analysis. It was only necessary for all patient subgroups to adhere closely to the inclusion-exclusion criteria in order to benefit from rt-PA. However, in patients over age 75 with NIHSS scores >20, the response to rt-PA was much less robust: only 10% had minimal or no disability at 3 months versus 2% of placebo-treated patients.[211] Other data, however, indicate that rt-PA benefit is lost in patients whose CT scans reveal more than one-third of a hemisphere is ischemic.[135,209] A low NIHSS score (less than 4) is another potential reason not to administer rt-PA if the neurological deficit is not disabling. The deficit often involves a small lacunar stroke that will improve on its own. The exception concerns patients with isolated aphasia or isolated hemianopsia in whom the low NIHSS score reflects neither the size of the lesion nor its functional importance. The investigators also found that the clinical benefit of rt-PA treatment observed at three months is sustained for a full year after stroke.[212] They also found that starting thrombolysis within 90 minutes of stroke onset had a better outcome profile compared to starting treatment between 90 minutes and 3 hours.[213] This last finding reinforced the concept of “time is brain” with respect to restoring cerebral perfusion promptly. However, there have also been several attempts to expand the three hour therapeutic window for intravenous rt-PA because the vast majority of patients arrive in the ED too late. In particular, MRI software has become increasingly sophisticated in its attempts to distinguish infarction from brain regions that are still viable (perfusion/diffusion mismatch) and that could benefit from rt-PA well after the three hour therapeutic window has passed.[214] However, there has yet to be a sufficient body of data to warrant a general recommendation that perfusion/diffusion mismatch or other combinatorial imaging modalities be routinely used to select patients for thrombolytic therapy.[135] Other data suggest that the average therapeutic window for most acute strokes may extend as far as 4.5 hours.[135] Several current studies are evaluating rt-PA and other thrombolytic drugs given after three hours of stroke onset. The ECASS III trial is a large, double-blind, placebo-controlled trial to test if intravenous rt-PA is useful when administered between three and four hours after stroke onset. The Third International Stroke Trial examining thrombolysis (IST-3) may offer additional information on longer treatment windows as well.[215]

Reteplase (Retavase), a genetically engineered tissue plasminogen activator shown to possess a longer plasma half-life, was approved by the FDA for the treatment of acute myocardial infarction. Three open-labeled and nonrandomized trials are currently evaluating the safety and efficacy of reteplase in acute ischemic stroke using either intra-arterial[216] or intravenous[217,218] administration. The ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation (ROSIE)[217] and ROSIE-CT[218] are examining the combined therapy of abciximab and intravenous reteplase. Patients with acute ischemic stroke from 3 to 24 hours of symptom onset will receive escalating doses of intravenous abciximab followed by intravenous reteplase. In addition to the defined primary clinical endpoints in ROSIE, ROSIE-CT will also examine the efficacy of cerebral reperfusion as measured by perfusion MRI and CT perfusion.

Tenecteplase (TNKase), another genetically engineered version of rt-PA shown to possess greater fibrin specificity and a longer plasma half-life than alteplase, was tested in a pilot dose-escalation, phase I trial. Tenecteplase given intravenously at doses of 0.1 to 0.4 mg/kg to patients within three hours of ischemic stroke onset was found to be safe.[136] Phase II and III randomized trials to test the safety/efficacy of tenecteplase are warranted.

Desmoteplase, a recombinantly manufactured form of the naturally occurring plasminogen activator in bat saliva, has an absolute dependence on fibrin for activity in contrast rt-PA. A phase II safety and efficacy trial of desmoteplase administered to acute ischemic stroke patients with perfusion/diffusion mismatch at three to nine hours after stroke onset was found to be safe (intracerebral hemorrhage rate of 2.2% compared to 0% for placebo treated patients) and effective (cerebral reperfusion of 71% in desmoteplase treated versus 19% in placebo-treated controls) at doses up to 125 µg/kg.[140] A phase III trial titled Desmoteplase in Acute Ischemic Stroke-2 (DIAS-2) was launched in 2005 but a preliminary report in June 2007 at the 16th European Stroke Conference in Glasgow, Scotland showed no benefit of desmoteplase with either a 90 µg/kg or 125 µg/kg dose.

Ancrod (Viprinex) depletes circulating fibrinogen thereby removing the substrate for thrombus formation and secondarily ancrod activates plasminogen. Ancrod has been tested in three small and two large randomized trials in patients with acute ischemic stroke. The Stroke Treatment with Ancrod Trial (STAT)[147] was a phase III, double-blind, placebo-controlled trial that randomized 248 patients within three hours of stroke symptoms to ancrod and 252 similar patients to placebo therapy. Ancrod was administered intravenously for 72 hours and then intermittently for two days. Favorable functional status, defined as the Barthel Index of >95 at three months, was achieved by 41% of the ancrod-treated group versus 35% in the placebo group; a difference that was significantly in favor of ancrod ($p = 0.04$). Symptomatic intracranial hemorrhages in the ancrod-treated group (5.2%) were not statistically higher than in the placebo group (2%).

A similar study design to that of STAT was employed in a larger (1222 patients) European study titled European Stroke Treatment with Ancrod Trial (ESTAT).[219] However, the treatment window in ESTAT was extended from the three hours used in STAT to six hours after stroke symptom onset. In ESTAT the great majority of patients began ancrod therapy between three and six hours in contrast to the STAT study in which ancrod was initiated in all patients before three hours. Unfortuneately, the primary clinical endpoint of the Barthel Index of >95 at three months was 42% in both the ancrod and placebo groups. Mortality (ancrod 20% versus placebo 14%) and symptomatic intracranial hemorrhage rates (ancrod 7.3% versus placebo 1.5%) were significantly higher in the ancrod group. These data indicate that ancrod is effective when given within three hours of stroke onset[147] but ineffective if the therapeutic window is extended beyond three hours.[219] Current treatment guidelines do not support the use of ancrod to replace intravenous rt-PA.[135]

Two additional studies, the Ancrod Stroke Program I and II (ASAP I, ASAP II) are ongoing phase III, randomized, placebo-controlled trials of intravenous ancrod administered in patients with NIHSS scores 5–25 and within six hours of stroke onset.[220]

Intra-arterial thrombolysis

To date, the FDA has not approved the intraarterial use of thrombolytics for acute ischemic stroke. However, intra-arterial thrombolysis is commonly used in many comprehensive stroke centers in the United States and is the subject of ongoing clinical investigation. In the current stroke management guidelines,[135] intra-arterial thrombolysis for acute ischemic stroke is described as an "option for treatment of selected patients with major stroke of <6 hours duration due to large vessel occlusion of the MCA and who are not otherwise candidates for intravenous rtPA."[135(p 1678)] In many stroke centers, patients with occlusions of any of the extracranial or intracranial cerebral arteries are offered the optional use of intra-arterial thrombolytics, especially if they have progressed beyond the three hour treatment window for intravenous rtPA therapy. Experience gained from the PROACT II trial has fostered a six hour intra-arterial thrombolytic treatment window for occlusions of the anterior cerebral arteries (ICA, ACA, MCA) and anecdotal reports have driven treatment windows extending out to 12 hours and longer at some centers for occlusions of the vertebral and basilar arteries. In any case the use of intra-arterial UK or rt-PA is potentially harmful and any deviation from current guidelines (Table 5–2) has the potential to shift the risk/benefit ratio towards greater harm. The risk/benefit profile of intra-arterial UK or rt-PA and the fact that neither is FDA approved for this use must be discussed with, and consent obtained from, the patient and/or family prior to treatment. Current treatment guidelines state "the availability of intraarterial thrombolysis should generally not preclude the administration of intravenous rt-PA in otherwise eligible patients.[135 (p 1678)]

Reteplase (Retavase) was reported to be undergoing a nonrandomized trial to evaluate escalating intra-arterial doses in combination with intravenous abciximab for recanalization of occluded cerebral arteries from three to six hours of stroke onset.[216] The status of the latter study is unknown.

Prourokinase (Prolyse), a recombinant form of high molecular weight urokinase (rp-UK), was tested successively in phase II and phase III studies titled Prolyse in Acute Cerebral Thromboembolism Trial I (PROACT)[221] and PROACT II.[144] Patients with angiographically proven occlusion of the MCA and stroke symptoms of <6 hours onset were randomized in a ratio of two to one to intraarterial rp-UK plus intravenous unfractionated heparin (UFH) versus UFH alone. Primary outcome measures included a modified Rankin Scale score of <2 at 90 days and recanalization of the MCA at two hours after initiation of infusion. The MCA was reopened in 66% of 121 patients treated with rp-UK plus intravenous UFH versus 18% in the intravenous UFHtreated group (p = .001). A modified Rankin Score of 2 or less was recorded in 40% of the rp-UK treated subjects but in only 25% of the UFH-treated control group at 90 days (p = 0.04). Symptomatic intracerebral hemorrhage within 24 hours of treatment was recorded in 10% of patients treated with rp-UK plus UFH versus 2% in the control group (p = 0.06). Mortality between the intra-arterial rp-UK plus UFH group (25%) and the intravenous UFH-only treated patients (27%) did not differ. Despite these positive results the FDA did not approve intra-arterial rp-UK for acute ischemic stroke because of the increased frequency of symptomatic intracerebral hemorrhage within the first 24 hours. In 1999, rp-UK was removed from the market due to manufacturing problems and has not been reintroduced.

Urokinase (Abbokinase), a recombinant form of low molecular weight urokinase, was tested in several small nonrandomized trials but is not approved by the FDA for cerebral artery thrombolysis. However, intra-arterial urokinase (UK) is frequently used off-label in many U.S. stroke centers. This practice is based largely on the PROACT II study results, other anecdotal reports, and the experience at these stroke centers that recanalization of occluded cerebral arteries is more frequently achieved with local intra-arterial versus intravenous administration of thrombolytic agents. However, angiographically proven recanalization success does not always correlate with clinical benefit after thrombolysis. An artery may be reopened yet not function efficiently. In contrast, good clinical outcomes may be achieved with persistent occlusion of a major artery due to successful thrombolysis in collateral arteries that perfuse the affected cerebral territory.[222]

Combination of intravenous and intra-arterial thrombolysis

The local application of lytic agents near or within the clot via arterial catheterization results in a significantly higher recanalization rate[142,144] compared to intravenous thrombolysis but the latter approach can be accomplished substantially more quickly. The time delay for transportation to an interventional neuroradiology suite and for catheter placement for intra-arterial thrombolysis are important disadvantages for this method of therapy. Retrospective analysis of the NIH rt-PA Trial[213] and results from ATLANTIS[223] demonstrate that patients treated within the first 90 minutes of stroke symptoms have a significantly better outcome than those treated after this time. To exploit the advantages and minimize the disadvantages of either intravenous or intra-arterial rt-PA administration the safety and feasibility of combining both approaches for acute stroke was first tested in the Emergency Management of Stroke (EMS) Bridging Trial.[224] The latter study and the Interventional Management of Stroke Study II (IMS)[225] have demonstrated the safety of combining this duel method of rt-PA administration. A study (IMS III), under the guidance of the IMS investigators, is underway to test the efficacy of combined intravenous and intra-arterial administration of rt-PA in acute stroke.

Antiplatelet Agents

Aspirin for acute stroke was tested in two large randomized trials, the International Stroke Study (IST)[226] and the Chinese Acute Stroke Trial (CAST).[227] Both studies showed a small positive (~1%) but significant effect of reducing early recurrence of stroke when aspirin was given within the first 48 hours of symptom onset. Small but significant increases in systemic hemorrhages were noted in both trials.

In patients not treated with thrombolytic agents, aspirin should be started at a dose of 325 mg once a day within the first 48 hours of stroke onset following the recommendations stated in the current guidelines.[135] When considering options for secondary stroke prevention the physician may elect to continue aspirin at doses of 325 mg or 81 mg once a day or switch to the combination of aspirin and extended-release dipyridamole (Aggrenox) 25 mg/200 mg twice a day, or clopidogrel (Plavix) 75 mg once a day.

IIB/IIIA platelet inhibitors

The FDA has approved the use of IIb/IIIa platelet inhibitors, abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat) for acute coronary syndromes but these drugs remain experimental for the treatment of acute ischemic stroke.

Abciximab (ReoPro), a IIb/IIIa platelet inhibitor, was studied in a small phase II and larger phase III trial in patients within six hours of stroke symptom onset.[228] The phase III study titled Abciximab in Emergent Stroke Treatment Trial (AbESTT II) was stopped prematurely because of a high rate of intracranial hemorrhage.

Eptifibatide (Integrilin) in combination with intra-arterial rt-PA was found to be safe in acute ischemic stroke with a trend toward improved arterial recanalization and clinical outcome in a small anecdotal study.[229] The combination of eptifibatide and intravenous Retavase are undergoing further study in ROSIE.[217]

Anticoagulants

For almost three decades, anticoagulation with intravenous unfractionated *heparin* was a common practice in acute stroke because many physicians strongly believed that clot propagation and stroke progression could be halted and outcome improved. Heparin in theory was supposed to arrest the growth of red thrombus, prevent its propagation and occlusion of stenotic arteries and thereby reduce the chance for embolization. The risk for hemorrhagic complications, however, including bleeding into the infarct, was of great concern. Several early studies without the benefit of CT scanning to exclude hemorrhagic stroke nevertheless suggested that heparin improved outcome when used emergently.[230] Lack of randomization, reliance on historical controls, and other methodological flaws undermined the conclusions. A large, randomized, placebo-controlled trial reexamined the benefit of IV heparin in acute stroke and found none.[231] However, most patients received heparin more than 24 hours after stroke onset when neurological deficits were usually stable and hence may have been treated too late. Thus, heparinization for acute stroke has been plagued with uncertainty and controversy regarding efficacy. The controversy subsided somewhat when in 1994, a panel appointed by the American Heart Association Stroke Council concluded that no convincing evidence existed that anticoagulants were effective in acute ischemic stroke, regardless of the arteries involved or the presumed etiology.[209] An earlier meta-analysis of heparin use in acute stroke had also found no improvement in neurological outcome although deep venous thrombosis (DVT) was clearly suppressed.[232] These reports dampened the enthusiasm for anticoagulation and refocused interest on thrombolytics for acute stroke and antiplatelet therapy for long term stroke prophylaxis. The current management guidelines do not recommend acute anticoagulation with heparin in the routine treatment of ischemic stroke.[135]

Despite lack of evidence regarding heparin efficacy in acute stroke, physicians occasionally do prescribe anticoagulation in special contexts. In each case, anticoagulation is used for stroke prophylaxis and not to treat the acute stroke. The dose of intravenous heparin is adjusted to achieve anticoagulation at 1.5–2 times baseline activated PTT or approximately 40–60 seconds. Anticoagulation may still be useful in the following scenarios.

1. Stroke attributed to cardioembolism and associated with atrial fibrillation, poor ventricular function (ejection fraction <30%), or thrombus visualized with echocardiography (e.g., mural thrombus, atrial clot, clot on a mechanical valve). Anticoagulation is a bridging therapy to warfarin until the International Normalized Ratio (INR) reaches a value of 2–3.
2. Symptomatic carotid artery stenosis before endarterectomy or stent placement.
3. Basilar artery thrombosis with progression of neurological deficits despite antiplatelet therapy.
4. Acute cervical artery dissection.
5. Progressing stroke despite antiplatelet therapy.
6. schemic stroke due to cerebral venous thrombosis.
7. Nonbacterial thrombotic endocarditis.

Relative contraindications to intravenous heparin include elderly patients (>80 years), systolic BP >185 mm Hg despite anti-hypertensive therapy, recent history of systemic or intracerebral hemorrhage, and allergy or other heparininduced complications.

Low-molecular-weight heparins

A meta-analysis of low-molecular-weight heparins (LMWH) in acute stroke[233] showed that venous thromboembolic events were diminished but extracranial bleeding was increased; combined death and disability was lower but did not reach statistical significance. Bath and colleagues[233] concluded that LMWH was of no benefit in the acute management of ischemic stroke. Low-molecular-weight heparins are not included in the current guidelines for the acute treatment of ischemic stroke.[135] However, when heparin and LMWH are administered subcutaneously to prevent DVT, these agents are effective and safe and should be given to bedridden patients at high risk for DVT and pulmonary embolism.

Therapy for hypertension

The blood pressure is frequently elevated in the early hours of acute stroke and may require urgent treatment if there is a major risk for acute end organ damage such as hypertensive encephalopathy, myocardial infarction, pulmonary edema, and acute renal failure. However, overly aggressive treatment of hypertension in acute stroke may decrease cerebral blood flow to the ischemic penumbra and cause neurological worsening. What should the clinician do when faced with hypertension in an acute stroke patient? The American Heart Association has issued guidelines to assist the physician in making such treatment decisions.[135] In many patients, hypertension is transient and reverses within a few hours after stroke onset without specific treatment. What level of hypertension mandates treatment is controversial. The AHA guidelines[135] suggest treatment if the systolic blood pressure is >220 mm Hg or the mean blood pressure is >120 mm Hg. When treatment is necessary, cautious lowering of the blood pressure by 15% within the first day is a reasonable goal. If the patient is a candidate for rt-PA, the blood pressure should be lowered to a systolic <185 mm Hg and diastolic <110 mm Hg before initiating thrombolytic therapy. The antihypertensive agent chosen should be able to reduce blood pressure quickly and yet permit a rapid reversal if the blood pressure drop causes neurological worsening. Recommended agents for use prior to rt-PA treatment include: Labetalol 10 to 20 mg IV infused over to 2 min (may repeat once), nitropaste 1 to 2 inches, and nicardipine 5 mg/hour (titrate up by 2.5 mg/hour at 5 to 15 min intervals, maximum dose 15 mg/hour, then reduce to 3 mg/hour). During thrombolytic treatment and for two hours after, the blood pressure should be checked every 15 min, then every 30 min for the next six hours and then every hour for 16 hours. For systolic blood pressures >180 mm Hg or diastolic >105 mm Hg, Labetalol 10 mg intravenously can be given every 10 to 20 min (maximum dose of 300 mg) or 10 mg intravenous can be followed by an infusion at 2 to 8 mg/min. If systolic blood pressure is >230 mm Hg or diastolic >120 mm Hg, Nicardipine can substitute for Labetolol at the doses described previously. If these measures do not control blood pressure, a sodium nitroprusside drip should be considered.

Therapy for hyperglycemia

Hyperglycemia, whether secondary to a stress response or to diabetes mellitus, is a common occurrence in acute stroke victims. Extensive experimental animal data and human studies agree that an elevated blood sugar at the time of focal brain ischemia is associated with a poorer neurological outcome and larger cerebral infarcts.[135] The mechanism underlying this detrimental effect may be a combination of enhanced tissue lactic acidosis, free radical production, and edema. There is consensus agreement (Class I data) that hyperglycemia in acute stroke patients should be treated with insulin and most recently the threshold blood sugar for treatment was lowered to a value >140 mg/dL.[135]

Conclusion

Effective therapy for acute ischemic stroke is currently available with the use of intravenous rt-PA within the first three hours of stroke symptom onset. However, only about 4% of patients with ischemic stroke have received intravenous rt-PA since its use was approved in 1996. The main limiting factor is the narrow therapeutic time window. No other treatments for acute ischemic stroke have yet demonstrated efficacy in clinical trials, although recent results with albumin are encouraging. The use of combination treatments is promising and is currently incorporated into several clinical trials for acute ischemic stroke, especially with the use of interventional techniques, such as mechanical thrombectomy. Other future trends may include the more timely administration of multiple neuroprotectants as a cocktail taken at home by a patient immediately at the first sign of stroke or administered by EMS en route to the hospital.

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Management of Elevated Intracranial Pressure

Chapter: Management of Elevated Intracranial Pressure
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Raised intracranial pressure (ICP) can significantly contribute to brain injury. It most often occurs as a result of acute neurologic insults, but it also exists as a chronic idiopathic condition. In the intensive care unit, elevated ICP is frequently associated with neurologic diseases including trauma, stroke, and intracranial hemorrhage as well as with systemic diseases such as hypertensive emergencies, hepatic failure, and a host of metabolic derangements. If untreated, elevated ICP can lead to further neurologic injury and death, whereas attention to ICP allows for the timely management of these life-threatening emergencies. A thorough understanding of ICP pathophysiology can help the clinician to identify patients with elevated ICP, and can guide rapid and informed decision making in the critical care setting. With that goal in mind, this chapter will review the normal physiology of ICP, discuss the mechanisms by which ICP can become disordered, and review the available treatment options.

Physiology

Monro-Kellie Doctrine

The normal adult intracranial vault is about 1400 to 1700 cubic centimeters (cc) in volume. As shown in Figure **6–1**, the intracranial space is filled by the brain (87%), cerebrospinal fluid (9%), and blood (4%).i The cerebrospinal fluid (CSF) is approximately equally divided between the ventricular and subarachnoid spaces, whereas the majority (70%) of intracranial blood is in the capillary and venous space, and only about one third is in the arteries.

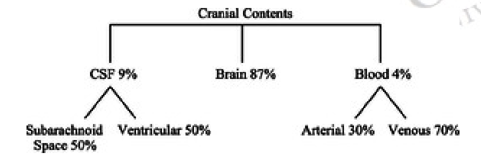


Figure 6–1.
The relative volume of the intracranial contents.

Alexander Monro first described the basic physical relationship between pressure and volume within the skull in 1783.[2] Specifically, he realized that the cranial vault represents a “rigid box,” and its contents are liquid or gelatinous, and therefore incompressible. Because of these two facts, any increase in the volume of the cranial contents will (1) increase the intracranial pressure, and (2) displace the normal cranial contents. This fundamental principle was later corroborated by Monro’s student George Kellie, and is now referred to as the Monro-Kellie doctrine.

The Monro-Kellie doctrine dictates that any increase in the volume of one of the contents of the skull will displace the other two. The relationship between the intracranial volume and ICP can be described as *elastance*, the change in pressure over the change in volume, which represents the elasticity of the intracranial contents. It may be more helpful to think of the inverse of elastance, *compliance*, which is the change in volume over the change in pressure. Compliance describes the reserve capacity of the intracranial compartment to accommodate increases in volume. Under normal conditions, the CSF, brain, and blood each provide some amount of compliance. The mechanism of

compliance for each of these elements will be described further on in this chapter. Because of multiple mechanisms of compliance, the change in pressure is not linearly related to changes in volume and pressure increases exponentially once the compensatory mechanisms are overwhelmed (Figure **6–2**).

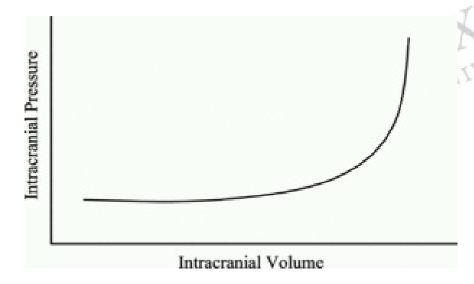


Figure 6–2.
Intracranial compliance. Changes in the volume of intracranial contents have little effect on ICP until the compensatory mechanisms are overwhelmed.[185] As ICP rises, first the CSF is displaced, then intracranial blood, and finally the brain is displaced.

Cerebrospinal Fluid Dynamics

Cerebrospinal fluid plays an extremely important role in protecting the brain and spinal cord. It allows these structures to float freely, making them much less susceptible to traumatic injury from mechanical shock. It also provides a mechanism of drainage of toxins and waste products, as the brain does not have a lymphatic system. Most relevant to this chapter, CSF provides compensation for changes in ICP.

Cerebrospinal fluid flow and pressure within the cranial vault is determined by production, circulation, and drainage.[3] Cerebrospinal fluid production takes place primarily in the choroid plexus (~60%). Here, CSF is the product of active ion transport. A sodium gradient is created by Na+/K+ ATPase, which allows a Na+/H+ antiporter to function. The proton pump creates an electrical gradient that is countered by the production of bicarbonate via carbonic anhydrase. This is a complex system that precisely regulates the intracellular pH, and results in the choroidal secretion of CSF. The remaining 40% of CSF production is extrachoroidal and passive, and takes place in the ependyma, brain parenchyma, and across capillary walls. The total rate of production is difficult to measure precisely, but is likely relatively constant at approximately 0.35 cc/min,[4] corresponding to roughly 20 cc/hour or 500 cc/day. Interestingly, the rate also seems to vary diurnally; production is at its peak around 2 am and it's slowest around 6 pm.[5]

From its production in the lateral and third ventricles, CSF flows through the cerebral aqueduct to the fourth ventricle, and then through the foramina of Luschka and Magendie into the subarachnoid cisterns. Here, CSF flows more slowly, going in both caudal and rostral directions. Caudally, it flows into the spinal subarachnoid space, where the thecal sac provides one important mechanism of ICP compliance. Rostrally, CSF flows into the cisterns surrounding the brainstem. After flowing around the cerebral hemispheres, CSF is resorbed by the arachnoid granulations of the superior sagital sinus and other mechanisms.

The CSF resorption in the arachnoid villi is via *passive transport*, and there appears to be a direct relationship between CSF pressure and its rate of resorption. Resorption begins at CSF pressures of <1 cm H2O, and increases linearly to a maximal rate of about 1.5 cc/min, which occurs at pressures of ~25 cm H2O.[6] This relationship results in equilibrium between production and resorption at pressures of approximately 1.1 cm H_2O. The CSF resorption in the arachnoid granulations provides another mechanism of compliance: when ICP is high, CSF is resorbed more quickly. However, this mechanism can be blunted with increasing pressure in the venous sinuses (see further on in this chapter). In addition to resorption via the arachnoid villi, a significant portion of CSF is transported directly into nasal mucosal lymphatics via the cribiform plate. Perhaps as much as 40% of CSF is drained into extracranial lymphatics under normal conditions.[7] Finally, a small amount of CSF may be directly resorbed through the walls of the capillaries in the central nervous system.[6]

Cerebrospinal fluid provides a dynamic system of compensation for rapid changes in ICP. Probably the largest component of CSF compliance is the distensible dural sac of the spine.[8] By this mechanism, CSF may ebb and flow through the foramen magnum with rapid changes in pressure, helping to maintain a relatively stable ICP. More prolonged increases in ICP likely recruit other CSF compliance mechanisms, including spinal lymphatic drainage and increased resorption via the arachnoid granulations.[9] Displacement and increased resorption of CSF are important elements of intracranial compliance. These mechanisms are rapid and have little pathologic sequelae, and are usually the first employed during changes in ICP.

Cerebral Blood Flow Dynamics

Stable blood flow is essential to normal brain function. Without regulation, increased ICP would cause a pathologic decrease in cerebral blood flow, and increased blood pressure would cause a pathologic increase in ICP. However, these variables are controlled by a variety of passive and active processes.

The cranium provides a rigid container with increased pressure compared to extracranial space. With every cardiac cycle, the pressure and relative volume of the cranial elements changes slightly. During systole, the arterial compartment expands. Per the Monro-Kellie doctrine, this volume expansion must result in the displacement of another intracranial element. The arterial pulsation is transmitted immediately to the surrounding fluid, largely CSF. The CSF then acts like a hydraulic piston, transmitting the pulsation to the remainder of the intracranial space. This pressure wave finds one of the most easily distensible components of the intracranial compartment; the subdural venous system, which collapses and thereby expels venous blood out of the skull and preserves the intracranial volume.

This demonstrates the importance of a patent cerebral venous drainage system. If venous drainage were impaired, increased resistance and hence increased cerebral blood volume (CBV) would result. The significance of venous resistance is demonstrated by the variability of ICP with head position. Simply by raising the head 30°, the cranial venous outflow is augmented, which decreases CBV and ICP can be reduced.[10]

In addition to these passive mechanisms, cerebral blood flow (CBF) and CBV are regulated by active processes. The regulation of CBF depends on a number of parameters outside the cranial vault: arterial pCO_2, arterial pO_2, arterial pH, and mean arterial pressure (MAP). The changes in CBF seen with changes in arterial pCO_2 are likely mediated by alteration of extracellular pH.[11] For every 1 mmHg change in pCO_2, there is an approximate 3% decrement in CBF.[12] This means that halving the normal pCO_2 from 40 to 20 mmHg effectively halves the normal CBF. This relationship between CBF and pCO_2 remains roughly linear through a range of pCO_2 from approximately 20 to 80 mmHg. In contrast, CBF does not vary with changes in pO_2 within the normal range. However, below 50 mmHg, CBF increases dramatically in order to deliver as much oxygen as possible to the deprived brain.

In addition to the partial pressures of oxygen and carbon dioxide, CBF is actively regulated relative to changes in MAP. Despite wide fluctuations in MAP, cerebral blood vessels display a remarkable ability to maintain nearly constant CBF. If CBF were not held constant, the brain would be subject to either ischemic or hyperemic insults. This is a process of *autoregulation*, wherein the resistance of cerebral blood vessels is altered in response to changes in arterial pressure. This relationship is described by the formula:

$$\mathrm{CBF} = (\mathrm{MAP} - \mathrm{JVP})/\mathrm{CVR}$$

where JVP is the jugular venous pressure and CVR is the cerebrovascular resistance. Because of autoregulation, CBF is stable across MAP ranging from approximately 50 to

150 mmHg (Figure **6–3**). Importantly, the autoregulation curve may be shifted to the right with chronic hypertension (Figure **6–3**). As a result, reducing the MAP too quickly in the setting of chronic hypertension can result in cerebral ischemia.

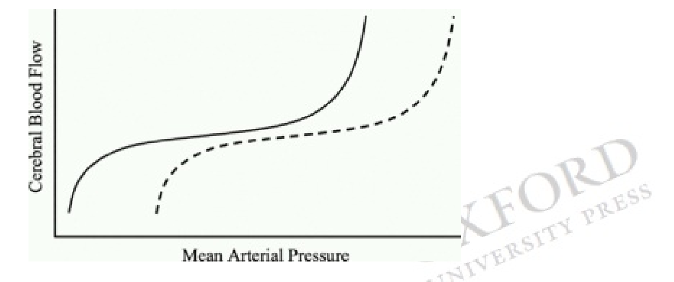


Figure 6–3.
Autoregulation of cerebral blood flow. In normal physiology (solid line), autoregulation allows CBF to remain stable across a range of MAP of approximately 50 to 150 mmHg. In chronic hypertension, autoregulation accomodates to the elevated blood pressure and shifts to the right (dotted line).

When relating the MAP to intracranial blood flow, the ICP must be taken into account. The arterial pressure within the cranial vault is known as the cerebral perfusion pressure (CPP) and is related to the MAP by the formula:

$$\mathrm{CBF} = \mathrm{MAP} - \mathrm{ICP}$$

CPP is therefore directly related to MAP and ICP. However, because the autoregulation of CBF is an active, dynamic process, the relationship between CPP and ICP is nonlinear. This concept is illustrated in Figure **6–4**. Very low CPP does not impact ICP, but provides inadequate cerebral blood flow (hypoperfusion). Cerebral perfusion pressure within the normal physiologic range, combined with normal autoregulation and compliance mechanisms, results in a constant ICP. When CPP is pathologically elevated, compensatory mechanisms are overwhelmed and intracranial hypertension ensues. This relationship is central to the management of raised ICP, because treatments can often be directed toward either correcting the CPP or ICP, and the clinician must decide which is the priority.

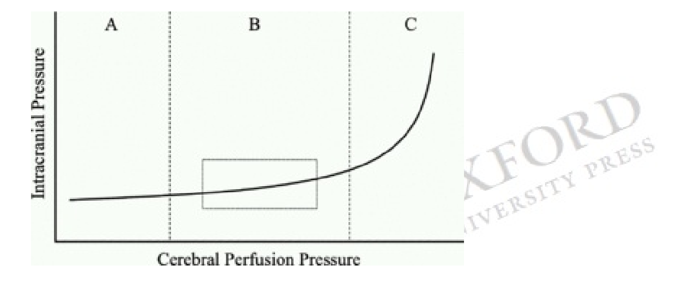


Figure 6–4.
The relationship between ICP and CPP is nonlinear. In zone A CPP is pathologically low (less than 50 mmHg). It has little effect on ICP, but provides inadequate cerebral blood flow and can result in ischemia. In zone B, CPP is within the normal range. Autoregulation and compliance function optimally at this pressure, and ICP remains stable. The rectangle represents the therapeutic goal. In zone C, CPP is pathologically elevated. Here, autoregulation and compliancs are overwhelmed, leading to elevated ICP.

Blood Brain Barrier

Aside from CSF and blood, the third principal constituent of the cranial vault is the brain itself. The brain matter is neither completely solid nor liquid; it can best be described as visco-elastic, meaning that it has properties both of a liquid and an elastic solid. As some neuropathologists say, it is the consistency of soft brie cheese. This physical property of the brain means that slow-growing mass lesions can lead to significant compression before compromising function. It also means that the brain is extremely susceptible to traumatic injury from impact forces. The brain's elastic properties also mean that it is capable of maintaining pressure gradients, sometimes over short distances. These gradients can be very detrimental and lead to brain herniation.

Much of the structural properties of the brain are dictated by its fluid content. Increased fluid content (edema) leads to increased ICP and further brain injury. The brain is unique in that it requires a specialized mechanism to tightly control its fluid and solute content. This is accomplished by the blood brain barrier (BBB), which is largely formed by capillary walls. Specifically, highly restrictive junctions between individual capillary endothelial cells, the zona occludens, impede the movement of ions and proteins into the brain. The BBB therefore restricts the passage of electrolytes and essential nutrients, such as glucose and amino acids. There are multiple transporters in the wall of the capillaries that actively transport these molecules into the brain. The constant active transport of nutrients into the brain requires large amounts of energy, which is reflected by the unusually high number of mitochondria within these endothelial cells. Because the BBB is formed by the lipid bilayer of cell membranes, lipid-soluble substances, such as water and gases, can easily diffuse across the BBB. This is particularly relevant to CNS iherapeutics; gaseous anesthetic agents work very quickly because they readily diffuse across the BBB, but hydrophilic systemic drugs such as antibiotics need to be given in higher doses if CNS penetration is desired.

By tightly controlling the passage of proteins and electrolytes between the intravascular and interstitial spaces, the BBB regulates the movement of water and hence brain volume. Normally, a steady-state between osmotic, hydrostatic, and oncotic pressures results in no net fluid exchange across the BBB. This equilibrium is described by the Starling equation, which depends on four main variables: the hydrostatic pressure gradient, the oncotic (and osmotic) pressure gradient, the permeability of water, and the reflection coefficient for solutes. The hydrostatic gradient is essentially the pressure difference between the intravascular blood pressure and the interstitial pressure, and contributes to the force driving water out of the capillary. This force is usually countered by the oncotic pressure, which results from different protein concentrations in the tissue and blood, and is in the range of 20–25 mmHg. Differences in oncotic pressure arise as a result of each solute's ability to cross the BBB, which is quantified as its reflection coefficient. A reflection coefficient of 1 means that the solute is unable to passively cross the BBB, and hence can create a substantial oncotic gradient. Solutes that can freely pass between the blood and tissue have a reflection coefficient of 0. In other organs, the oncotic gradient is a result of differences in protein concentrations. But because the BBB is specialized to limit the permeability of all solutes (including small ions), substantial oncotic and osmotic gradients can exist in the brain. As we will see later, these gradients become particularly important in the pathology of edema as well as the application of osmolar therapies for lowering ICP.

Pathophysiology

Intracranial compliance is provided by the CSF, blood, and brain. Displacement of the CSF likely does not cause harm, and occurs frequently during normal changes in the volume of intracranial contents caused by coughing, Valsalva maneuvers, and changes in head position. These physiologic events are easily compensated for by normal

compliance, and therefore ICP remains low and stable, on the left part of the curve in Figure **6–2**. As the volume of intracranial contents rises further, first venous and then arterial blood is forced out of the skull. This represents the limits of normal intracranial compliance, and ICP begins to rise exponentially. If it is allowed to continue to rise, this pathologically elevated ICP finally results in displacement (herniation) of brain tissue.

Cerebral Perfusion

As described above, CPP is inversely related to ICP. As long as MAP and ICP remain within the normal range, then CPP is adequate. Normal adult MAP of 75–90 mmHg and ICP of <15 mmHg results in normal CPP of 60–90 mmHg. Within this range, autoregulation keeps cerebral blood flow very stable despite fluctuations in CPP. However, pathologic increases in ICP can lead to insufficient CPP and result in hypoperfusion and infarction.

Normally, variations in both ICP and MAP are blunted by physiologic autoregulation to keep cerebral perfusion stable. With intracranial disease, autoregulation can fail and ICP can become pathologically elevated. When ICP rises beyond 20 cm H_2O, CPP can become insufficiently low, leading to brain hypoperfusion and infarction. The impact of elevated ICP on CPP may be global or local. In the case of focal mass lesions, locally elevated pressure can lead to insufficient perfusion and secondary ischemia via direct compression.[13] In other instances, diffusely elevated ICP can cause global cerebral hypoperfusion and ischemia.[14] These observations have some bearing on patient management. For example, maintenance of CPP of >70 mmHg in patients with severe head trauma and elevated ICP seems to result in improved outcomes.[15] However, there may be an increased risk of pulmonary complications if aggressive measures are required to augment blood pressure. Balancing the improved outcomes associated with higher CPP and its potential risks, the Brain Trauma Foundation (BTF) recommends that the CPP should be maintained at a minimum of 60 mmHg in severe traumatic brain injury.[16]

Just as ICP can adversely effect cerebral perfusion, a pathologically elevated CPP can cause raised ICP. This occurs most commonly in the setting of an elevated MAP as with systemic hypertension. The ensuing increase in cerebral perfusion leads to increased ICP and hypertensive encephalopathy. The elevated CPP also leads to increased hydrostatic pressure, which can in some instances promote increased diffusion of water across the BBB and lead to edema formation and the syndrome of posterior reversible leukencephalopathy.

Normally, physiologic autoregulation maintains stable cerebral blood flow across a wide range of CPP (Figure **6–3**). In patients with chronic hypertension, the autoregulatory curve shifts to the right in order to accommodate higher blood pressures and CPP.[17] This shift of the autoregulatory curve results in impaired tolerance of sudden decrements in CPP, such as could be precipitated with the acute treatment of hypertension. For this reason, rapid reduction of blood pressure in patients with chronic hypertension should be avoided, as it could produce cerebral ischemia.

In the setting of certain diseases, particularly those that disrupt the vasculature such as stroke or trauma, autoregulation can fail altogether. In these circumstances, the relationship between cerebral blood flow and CPP becomes linear. In this setting, minute changes in CPP can result in dramatic swings in CBF, and close attention and management of MAP is required.

Brain Edema

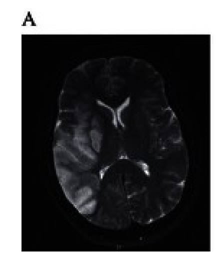
Brain edema is an increase in water and sodium content, leading to increased brain volume. It is the result of a multitude of disease processes, and can cause increased ICP, brain dysfunction, compression, and herniation. For almost four decades, brain edema has been conceptualized in two categories: cytotoxic and vasogenic.[18] Significant overlap exists between the two, but individual diseases are commonly predominated by one or the other type of edema.

Cytotoxic edema is the intracellular accumulation of water with consequent cellular swelling and occurs in neurons, glia, and endothelial cells within the brain. Cytotoxic edema is classically associated with acute infarction, but may also be caused by trauma, certain toxins, and osmotic disequilibrium. During tissue ischemia, normal cellular energy metabolism fails, and ATP is depleted within four minutes.[19] This leads to ion pump failure, and loss of normal cellular homeostasis. The ensuing loss of osmotic gradients results in net influx of water into the intracellular compartment, and cell swelling. Further cytotoxic events ensue, including lipolysis and release of glutamate, ultimately resulting in cell death. Cytotoxic (cellular) edema can also result from acute changes in osmotic equilibrium, such as those caused by hyponatremia or rapid correction of chronic hyperosmolar states. For instance, diabetic ketoacidosis results in hyperosmolality of the plasma, which promotes accumulation of compensatory organic osmolytes (ideogenic osmoles) within the cell to maintain normal osmotic gradients. In this circumstance, rapid correction of the plasma hyperosmolality can result in a new osmotic gradient secondary to residual intracellular osmolytes and subsequent cellular edema.[20] Although there are a number of causes of cytotoxic edema, the unifying mechanism is abnormal osmotic gradients across the cell membrane resulting in the intracellular accumulation of water.

In contrast, vasogenic edema is the extracellular accumulation of water in the brain. It is thought to occur as a result of blood vessel leakage, and is seen predominantly in the white matter. As discussed previously, the BBB normally works to exclude solutes from the brain, thus tightly controlling osmotic and hydrostatic homeostasis. When the capillary walls are damaged, ions, proteins, and fluid are allowed to leak into brain tissue. Breach of the BBB may occur through a variety of mechanisms including trauma, toxins, and infarction, but the most common is inflammation, usually resulting from infection or neoplasia. Inflammatory cytokines, such as TNF-alpha and interleukin-6, proteases released by white blood cells, and other inflammatory mediators can cause damage to the capillary wall and the extracellular matrix.[21] Breakdown of the BBB allows fluid accumulation in the extracellular space. Failure of the tight junctions between endothelial cells unhinders the hydrostatic force within the capillary and allows fluid to leak into brain tissue.

While both vasogenic and cytotoxic edema can and do occur simultaneously, many clinical syndromes are classically associated with one type. Vasogenic edema occurs more frequently in the setting of tumors and infections, whereas cytotoxic edema is characteristic of acute stroke and osmolar disequilibrium. The two types of edema are readily differentiated on the basis of magnetic resonance imaging (MRI) (Figure **6–5**); diffusion-weighted imaging is particularly sensitive for cytotoxic edema, while vasogenic edema can be identified by its morphology. The distinction between vasogenic and cytotoxic is important, as different treatment modalities can and must be employed for each type of edema.

A



B

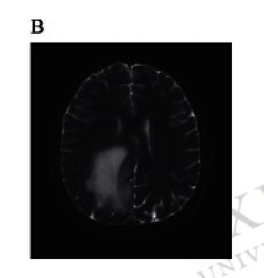




Figure 6–5.
Two T2-weighted MR images exemplifying brain edema. (A) Cytoxic edema associated with an infarction resulting from occlusion of the right middle cerebral artery. The edema involves the gray and white matter equally. (B) Vasogenic edema of the right parieto-occipital subcortical white matter resulting from a tumor. The vasogenic edema is predominantly in the white matter, giving the appearance of finger-like projections into the occipital gray matter.

In addition to cytotoxic and vasogenic there is a third type of edema—hydrocephalic or transependymal edema. When normal CSF flow is obstructed, pressure increases within the ventricles. This obstructive hydrocephalus creates a hydrostatic pressure gradient across the ventricular walls, and CSF begins to infiltrate the ependyma and accumulate in the periventricular brain tissue. In contrast to vasogenic and cytotoxic edema, hydrocephalic edema does not imply cellular damage unless very advanced.

Clinical Syndromes

There are many causes of increased ICP, ranging from chronic to acute (Table 6–1). Some of the acute etiologies include ischemic stroke (cytotoxic brain edema), hemorrhage, trauma, venous sinus thrombosis, and obstructive hydrocephalus. The acute causes of raised ICP tend to cause more symptoms, as many of the mechanisms of compliance discussed above are unable to compensate for rapid changes in ICP. Chronic causes of increased ICP include tumors (vasogenic edema), communicating hydrocephalus, liver failure, and toxins. The chronic disorders tend to cause less symptoms, or to present more slowly, due to improved compliance over time. For instance, a slow growing tumor gives the brain time to adapt to new pressure gradients, and slow focal compression is much less symptomatic compared to a rapidly accumulating space-occupying lesion of the same size. There is, of course, a spectrum of time courses of raised ICP. Some of the more subacute etiologies for increased ICP include infection (such as meningitis and abscess) and inflammatory disorders like neurosarcoidosis. The duration of symptoms is often helpful in elucidating the cause of elevated ICP.

Table 6–1 Causes of Elevated ICP
Acute etiologies
Brain trauma
Ischemic stroke
Intracerebral hemorrhage
Intraventricular hemorrhage
Epidural hematoma
Subdural hematoma
Intraventricular hemorrhage
Obstructive hydrocephalus
Venous sinus thrombosis
Fulminant hepatic failure
Meningitis Encephalitis
High-altitude cerebral edema
Hypertensive crisis
Subacute and chronic etiologies
Tumor
Abscess
Obstructive hydrocephalus
Communicating hydrocephalus
Idiopathic intracranial hypertension
Normal pressure hydrocephalus

Increased ICP may be focal or global. Localized lesions, such as abscess and tumor, present with focal neurologic findings corresponding to brain dysfunction in the region of the lesion. As the increased pressure is transmitted to the rest of the intracranial compartment, symptoms of generalized increased ICP begin to develop. Causes of globally increased ICP include hypoxic-ischemic insults, hydrocephalus, and metabolic derangements. Focal neurologic signs are often absent (at least initially) in these disorders.

The symptoms and signs of globally elevated ICP include headache, nausea, vomiting, visual changes, ataxia, mental status changes, and palsies of the sixth cranial nerve (Table 6–2). When severe, increased ICP may lead to Cushing's triad: the constellation of bradycardia, respiratory distress, and hypertension.[22] Cushing's triad is thought to be due to medullary dysfunction, and is an ominous clinical indicator of catastrophically elevated ICP. In cases of subacute or chronically elevated ICP the pressure is transmitted to the optic nerve and causes impaired axonal transport, resulting in papilledema. The fundoscopic exam is therefore a critical part of the neurologic exam, particularly in the setting of other symptoms or signs of elevated ICP. The signs of increased ICP may or may not present in combination with focal neurologic signs, depending on whether the cause is focal or diffuse.

Table 6–2 Symptoms of Elevated ICP
Headache
Nausea
Vomiting
Visual changes
Ataxia
Mental status changes
Abducens nerve palsy



As ICP continues to rise, pressure gradients within the cranial vault can become larger and lead to shifts of brain tissue known as herniation, which occurs in several stereotyped syndromes. *Uncal herniation* refers to the medial displacement of the uncus past the tentorium cerebri, and is associated with unilateral lesions of the temporal or frontal lobe, basal ganglia, or thalamus. As the medial temporal lobe is pushed into the perimesencephalic cistern, the oculomotor nerve may be compressed. This results in the first and best known clinical manifestation of uncal herniation—a dilated ipsilateral pupil. Also within the perimesencephalic cistern, the posterior cerebral artery may be compressed and result in ipsilateral infarction. Further herniation leads to lateral displacement of the midbrain, which may be pressed into the contralateral tentorial edge (Kernohan's notch). This results in a false localizing sign, because the contralateral cerebral peduncle is compressed and results in weakness ipsilateral to the lesion.[23] Finally, further pressure on the brainstem leads to more cranial nerve dysfunction, Cushing's triad, and death. Diffuse edema of the cerebral cortex, or bilateral space occupying lesions, may lead to the downward *central herniation* of the midbrain past the level of the tentorium. Compression of the brainstem leads to progressive cranial nerve palsies: there is bilateral pupillary dilation, loss of eye movements and the oculoce-phalic reflex, and loss of the corneal reflexes. Dysfunction of the reticular formation leads to coma. As central herniation continues, respiratory failure and hemodynamic collapse ensue. Additionally, downward herniation of the midbrain can lead to impaction of the brainstem and cerebellar tonsils in the foramen magnum, leading to the obstruction of CSF flow. This obviously can lead to catastrophic increased ICP, and usually has dire consequences if not corrected immediately. Both uncal and central herniation (the transtentorial herniations) have historically been regarded as harbingers of imminent death.[24] However, it is important to realize that these syndromes are reversible with immediate and aggressive treatment,[25] as outlined in the next section.

Lateralized lesions of the frontal or parietal lobes can lead to *subfalcine herniation*, which refers to a shift of the cingulate gyrus, below the falx cerebri, into the contralateral hemisphere. As the cingulum presses into the inter-hemispheric cistern the anterior cerebral artery may be compressed and cause infarction of the ipsilateral medial frontal lobe with consequent contralateral leg weakness. The precursor of subfalcine herniation can be measured on CT or MR imaging as the extent of the midline shift of the septum pellucidum. This provides a method of quantifying the ICP gradient, and the presence of a midline shift often portends worse prognosis.[26]

In addition to raised ICP secondary to intracranial disease, there are primary idiopathic disorders of increased ICP: idiopathic intracranial hypertension (IIH) and normal pressure hydrocephalus. Idiopathic intracranial hypertension, or pseudotumor cerebri, is a disorder of elevated ICP that occurs most commonly in obese women, and can frequently lead to visual loss. It is defined as a syndrome of increased ICP without an identifiable cause. Although described over 100 years ago,[27] the etiology remains unknown. Theories of its pathophysiology include excess CSF production, reduced CSF absorption, and increased cerebral venous pressure.[28] The most common presenting symptom is headache in 68%–98%, followed by visual changes in 52%–72% of patients with IIH. Visual symptoms are most commonly transient scotomata, but may include diplopia, flashes of light, and progressive constriction of the visual field. Patients may also complain of pulsatile tinnitus. On examination, the most common sign is papilledema, usually bilateral. Decreased visual acuity and sixth nerve palsies are also frequent findings, and formal visual field testing usually reveals enlargement of the physiologic blind spot. If untreated, IIH can cause progressive visual loss. The diagnosis rests on elevated ICP (above 20 or 25 cm H_2O) as measured by lumbar puncture manometry, in the absence of any identifiable etiology.[28]

The other common chronic disorder of ICP is normal pressure hydrocephalus (NPH). Clinically, NPH is thought of as a triad of gait apraxia, dementia, and urinary incontinence. The gait disturbance most often manifests as imbalance and falling, and seems to be the most common reason patients present for evaluation.[29] The dementia of NPH is nonspecific, but is usually characterized by slowed thought, amnesia, visuospatial impairment, and apathy. The urinary incontinence of NPH is also nonspecific, and is usually described as urgency and frequency. The pathophysiology of NPH is not well understood, but is thought to involve a disruption of CSF outflow or resorption. This causes increased pressure within the CSF, which leads to ventriculomegaly. It is thought that as the ventricles expand, the pressure returns to nearnormal levels. This is the reason that normal pressures are usually observed during lumbar puncture manometry in patients with NPH. The diagnosis of NPH therefore usually cannot be made by lumbar puncture alone. Rather, many groups employ tests of CSF physiology to make the diagnosis. Impaired CSF outflow resistance as measured by infusion of artificial CSF, intermittently raised ICP seen during continuous pressure monitoring with a lumbar catheter, and the clinical response to removal of a large volume of CSF, can all identify those patients with NPH and who may respond to treatment.[30] Making the diagnosis of NPH is important because, although the symptoms are seen in a variety of disease states, NPH is much more treatable than most other causes of dementia.[31]

Icp monitoring

Indications

As Table 6–1 suggests, elevated ICP can be caused by a myriad of diseases. Increased ICP can often lead to further neurologic deterioration and death, and reversing increased ICP can improve outcomes. Therefore, ICP monitoring can be critical to treating those patients at risk for elevated ICP and its consequences. However, most monitoring techniques are highly invasive and carry their own risks of complications. Thus, the decision to monitor ICP is usually individualized for each patient, based on the relative risk of symptomatic elevated ICP versus the surgical risks. In general, invasive monitoring should be considered for patients with any of the conditions listed in Table 6–1 who present with altered mental status or abnormal brain imaging, or who exhibit neurological deterioration.

Intracranial pressure monitoring is typically pursued when precise estimations of CPP are required. In this setting continuous monitoring of both ICP and MAP are obligatory, necessitating the use of an ICP monitor as well as an arterial catheter. Changes of either the ICP or MAP may lead to changes in the CPP, and manipulation of the systemic blood pressure and reduction of the ICP may both be necessary to optimize CPP. As discussed previously, CPP should ideally be maintained above 60 mmHg in order to meet cerebral metabolic demands in the setting of elevated ICP.[15,16]

One of the most common and best studied indications for invasive ICP monitoring is traumatic head injury. The BTF recommends ICP monitoring in severe head trauma with an abnormal CT and an initial Glasgow Coma Score less than 9. If the initial head CT is normal, the BTF recommends ICP monitoring with at least two of the following: age over 40, motor posturing (unilateral or bilateral), or systolic blood pressure <90 mmHg.[26]

Beyond traumatic brain injury, no formal guidelines exist as to when ICP monitoring should be employed. However, there are a number of other clinical scenarios in which the benefits of ICP monitoring may outweigh the risks of device insertion. For example, patients with subarachnoid hemorrhage may suffer severely increased ICP, and seem to

benefit from aggressive treatment of ICP and hydrocephalus.[32] Monitoring and treatment of elevated ICP in venous sinus thrombosis may also improve outcomes.[33] Patients with large strokes do not seem to benefit from ICP monitoring, although they may benefit from early intervention (like hemicraniectomy) to avoid severely increased ICP.[34] Intracerebral hemorrhage can cause significant elevation of ICP, and monitoring and CSF drainage can be particularly useful when intraventricular hemorrhage results in acute obstructive hydrocephalus. In addition to the numerous acute indications, ICP monitoring is frequently employed in the diagnostic work up of NPH.[31]

ICP Monitoring Devices

Although there are a number of devices that allow real-time measurement of ICP, the external ventricular drain (EVD) remains the gold standard as it is considered the most precise and accurate. The technique of real-time monitoring of ICP using an EVD has been in place since 1951.[35] Aside from pressure monitoring, the EVD has the additional ability to drain CSF, which is particularly useful in cases of hydrocephalus. Placement of the EVD is via a burr hole in the calvarium, through brain tissue, and into the CSF space of the lateral ventricle. The distal portion of the EVD is fenestrated to allow open communication of the CSF and fluid within the catheter. The fluid within the catheter transmits pressure to the extracranial portion, where it can be measured with an electronic transducer. Despite its advantages, however, the EVD does carry significant risks. The most common complication of EVD placement is infection, the incidence of which seems to rise sharply with EVD duration greater than five days.[36] For this reason, many surgeons use prophylactic antibiotics at the time of insertion, although published data in support of this practice are lacking. Other significant concerns associated with EVD use are injury to brain parenchyma, shift of intracranial contents secondary to altered ICP dynamics, and hemorrhage.

Aside from the EVD, several other monitoring devices are employed. The subarachnoid bolt (Richmond bolt) represents another option for direct fluid-coupled monitoring of ICP, but lacks the advantage of drainage capability. This system communicates with the subarachnoid CSF via a burr hole in the skull overlying a perforation in the dura. This is somewhat less invasive than the EVD, and carries less risk of infection and hemorrhage. However, subarachnoid bolts are not as accurate as EVDs, and are prone to plugging.[37] Lumbar catheters also provide a method of both pressure monitoring and drainage, although they don't directly measure ICP and increase the risk of herniation in intracranial disease. In contrast to these fluid-coupled systems, there are a number of solid-state devices available for ICP monitoring. These include strain-gauge and fiberoptic transducers that can be inserted into the epidural space, subarachnoid space, brain parenchyma, or ventricles. These systems may be more accurate than fluid-coupled techniques at the time of insertion, but pressure readings have a tendency to drift and cannot be re-zeroed and CSF cannot be drained. For this reason, solid-state devices are occasionally inserted along with an EVD. Finally, noninvasive techniques for ICP monitoring are in development, and include tissue resonance analysis,[38] transcranial Doppler,[39] tonometry of the fontanelle in children,[40] and others. None of these devices has yet proven to be as accurate as invasive ICP monitoring, and none provide the therapeutic value of the EVD.

All invasive devices for ICP monitoring depend on the notion that pressure is equally transmitted throughout the intracranial compartment. However, intracranial pressure dynamics may be a bit more complicated than this simplistic assumption based on the Monro-Kellie doctrine.[41] As early as 1902, Harvey Cushing noted that the pressure effects of intracranial mass lesions are greatest in the vicinity of the lesion.[22] It is now established that different brain areas transmit pressure differently. For example, the white matter seems more compliant than gray matter, and different areas of the cerebrum may transmit pressure differently. For this reason, a model of at least five different ICP compartments—the frontal lobes, the temporal lobes, and the occipital region—may better describe the transmission of pressure within the skull. The differences between these compartments may become clinically relevant when a mass lesion is greater than 25 cc in size or causes midline shift. In these circumstances, bihemispheric ICP monitoring could be considered.[41] However, insertion of more than one ICP monitoring device significantly increases their inherent risks. Nonetheless, one should at least bear in mind that pressure measurements with these devices represent local pressure, which may not reflect pressure gradients or global ICP.

Waveform Dynamics

The normal ICP in adults is 5–20 cm H_2O (5–15 mmHg) and is dynamic, changing from moment to moment with each pulse, respiration, head movement, valsalva maneuvers, and so forth. Sustained elevations above 20 cm H_2O are considered pathologic. When observed continuously, the ICP waveform varies with each cardiac cycle. The interaction of intracranial compliance and arterial pulsations produces a characteristic pattern comprised of three waves: the percussion wave (P1), the tidal wave (P2), and the dicrotic wave (P3). As shown in Figure **6–6**, P1 results from the arterial pulsation and is normally the sharpest and highest in amplitude of the three waves. When ICP rises and intracranial compliance is reduced, the P2 wave becomes elevated and eventually obscures P1. The pattern of P2 > P1 is suggestive of poor compliance, especially if a change from a larger P1 and smaller P2 to a smaller P1 and larger P2 is observed. Other changes in the ICP waveform may be caused by hypertension, hypotension, cerebral vasoconstriction, hypercapnea, jugular compression, and ICP lowering treatments.[42]

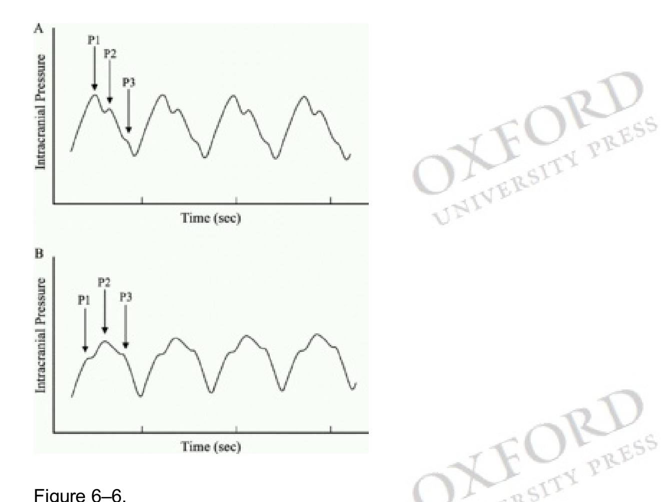


Figure 6–6.
ICP waveforms associated with the cardiac cycle. (A) The normal ICP tracing reveals three waves. The percussion wave (P1) is normally the highest in amplitude, and corresponds to arterial pulsations. (B) The diminished intracranial compliance associated with pathologically elevated ICP results in amplification of the P2 wave, which eventually buries P1 in its upslope.

Over slightly longer time frames, other patterns of ICP emerge. These waveforms were first described in detail by Lundberg as three distinct patterns: A-, B-, and C-waves (Figure **6–7**).[43] A-waves are always pathologic. Also known as plateau waves, A-waves consist of sustained elevations of ICP above 70 mmHg, lasting for 5 to 20 minutes. They usually end with an abrupt drop to baseline or below and frequently signify a catastrophic intracranial event, such as cerebral herniation. B-waves are rapid elevations in ICP occurring 0.5 to 2 times per minute. They are suggestive, but not definitive evidence of pathologic intracranial compliance. B-waves can be caused by autoregulatory changes in cerebral arteriolar tone. C-waves, or Traube-Hering-Mayer waves, can occur in normal individuals and are related to variability in MAP. They can occur 4 to 8 times per minute, and are typically very low in amplitude.

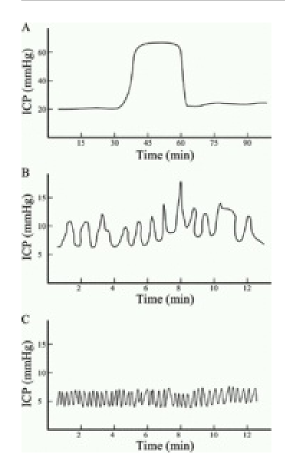






Figure 6–7.
Lundberg waves. (A) the Lundberg A-wave, or plateau wave, is seen as a rapid and sustained elevation in ICP to 70 mmHg or more. A-waves are associated with very poor intracranial compliance, and may be caused by cerebral vasodilation. (B) Lundberg B-waves are shorter and lower in amplitude than A-waves. They are associated with changes in cerebral blood volume. They are suggestive but not pathognemonic of reduced compliance. (C) Lundberg C-waves are low-amplitude, high frequency oscillations that occur in normal individuals and probably relate to blood pressure.

With highly accurate ICP monitoring, such as with solid-state transducers, spectral analysis of the ICP waveform can provide additional information about intracranial compliance. An index of compensatory reserve (RAP) can be generated using these data when averaged over several minutes. These mathematical techniques may provide important information about ICP pathophysiology and intracranial compliance,[3] although they are not yet in widespread clinical use.

Medical management

General Principles

The goal of ICP monitoring and treatment is to improve outcomes by maintaining adequate CPP, and avoiding brain herniation and injury secondary to elevated ICP. Given its dire consequences, elevated ICP should always be regarded as a medical emergency, and be treated swiftly and aggressively. Fortunately, there are a number of treatment options that lower ICP, and they will be reviewed in this section. In general, these treatments utilize four strategies—reducing brain volume and edema, reducing CSF volume, reducing cerebral blood volume, and treating the lesion itself. Many treatments make use of more than one of these strategies. The approach to each patient should be methodical, with particular focus on identifying the cause of elevated ICP, as some conditions respond better to certain types of treatment than others. Nonetheless, there are some general principles that should be considered in the approach to every patient suspected of having elevated ICP.

As always, the approach to the patient with potentially elevated ICP begins with attention to the airway, respiratory status, and cardiovascular function. However, certain maneuvers, such as endotracheal intubation, have the potential to increase ICP even further. Therefore, caution should be exercised in ensuring appropriate anesthesia and/or paralysis prior to intubation. Additionally, care should be taken to avoid compression of the neck veins as can occasionally occur during intubation or securing the endotracheal tube after insertion. Seizures increase the metabolic demand of the brain and can transiently raise ICP, so some advocate early use of prophylactic antiepileptic drugs in brain trauma.[26] Attention should also be given to maintaining normothermia, as fever increases brain metabolism and is a well-recognized contributor to poor outcomes. Acetaminophen and cooling blankets should be used liberally in patients with elevated ICP to avoid hyperthermia. Hyperglycemia should also be aggressively treated, as it is associated with worse outcomes in many critical disease states.[44]

Blood pressure control is especially important for patients with elevated ICP. In particular, systemic hypotension leads to poor outcomes in brain trauma[45] and can cause elevated ICP by way of autoregulatory vasodilation. Lundberg first postulated that cerebral vasodilation might underlie the severe elevations in ICP typified by A-waves.[43] In 1984, Rosner and Becker confirmed Lundbergs suspicion and showed that systemic hypotension resulting in decreased CPP can precipitate A-wave ICP elevations.[46] Hypotension can also be deleterious in cases of focally increased ICP, where decreased CPP can lead to local ischemia. Hypertension may also contribute to further brain injury in elevated ICP. Systemic hypertension in combination with breakdown of the BBB results in the rapid accumulation of vasogenic edema secondary to increased hydrostatic pressure, which further increases ICP. Likewise, hypertension in the setting of autoregulatory dysfunction leads to an immediate increase in ICP due to the lack of compensatory cerebral vasoconstriction. When autoregulation remains intact, hypertension must be treated cautiously if it is chronic, as abrupt lowering of the blood pressure could result in cerebral hypoperfusion (Figure **6–3**).[17] In general, the goal of blood pressure management should be to maintain CPP >60 mmHg,[16] which can be accomplished with fluid resuscitation and the use of pressors if necessary.[15] However, the use of fluids and pressor agents carry their own risks (including acute respiratory distress syndrome), and blood pressure management should be individualized to each patient.

Given the multifactorial approach to the patient with elevated ICP, many institutions have developed treatment algorithms that incorporate all of these variables.[47,48] Regardless of the protocol used, early recognition of elevated ICP and careful management of these patients will provide the greatest chance of survival. The importance of aggressive treatment of elevated ICP has been demonstrated by Qureshi and colleagues,[25] who have shown that herniation is reversible with early treatment. This has led to the *brain code* approach to cerebral resuscitation, just as a code blue delivers emergent treatment in the case of cardiopulmonary collapse. These systems encourage multidisciplinary readiness for the rapid recognition and management of raised ICP, and depend on an awareness of the acute treatment modalities described herein.

Hyperventilation

As discussed previously, CO_2 is a potent vasodilator in the cerebral vasculature, and lowering the arterial pCO_2 can lead to a rapid decrease in cerebral blood volume. Quantitatively, there is nearly a 3% decrease in CBF with every 1 mmHg reduction in pCO_2.[12] The intracranial blood volume decreases and consequently lowers the ICP. The effects of hyperventilation on ICP are transient, lasting from only four to six hours, after which the vascular tone accommodates to the new pH. For this reason, ventilation must be slowly normalized after hyperventilation, as a rapid return to normocapnea could result in rebound elevation of ICP.[49]

Despite its clear effect on ICP, hyperventilation has never been shown to improve outcomes. In addition, hyperventilation works by constricting cerebral blood vessels and has the capacity to cause ischemia. There is evidence that even moderate reductions in pCO_2 lead to hypoperfusion, and cerebral ischemia results when pCO_2 reaches 10 mmHg.[12] For this reason, ICP management with hyperventilation is usually performed only for brief periods, and the pCO_2 should not be reduced beyond 2530 mmHg. Chronic hyperventilation should be avoided. Hyperventilation should also be avoided in the first 24 hours after head trauma, as it can worsen perfusion when CBF is already compromised.[26,50]

Because reduced CBF with hyperventilation depends on intact autoregulation, some postulate that injured brain areas may experience less vasoconstriction and hence be

spared from further hypoperfusion. However, this is not the case. Despite disruption of normal CBF autoregulation in areas of brain injury, the effect of hyperventilation on global ICP remains intact.[51] In local areas of injury with baseline hypoperfusion, hyperventilation seems to increase the area of hypoperfusion. Hence, hyperventilation seems to increase the amount of brain at risk, although at pCO_2 levels of 25–30 mmHg it does not seem to result in actual infarction.[52] In an animal model of traumatic brain injury, hyperventilation contributed to increased neuronal death in hippocampus.[53]

With the serious concerns and limitations of hyperventilation, this therapy for elevated ICP should be used for brief periods of time only. Although no data exist to support its role in improving outcomes, hyperventilation does play a role in the acute management of elevated ICP. It should be considered as one of the first line rescue therapies in a brain code situation, until more definitive treatment can be initiated. If used, hyperventilation should maintain the pCO_2 at 30 mmHg for a maximum of six hours, and should never be used chronically or as ICP prophylaxis.

Positioning

Head elevation to 30° above horizontal should also be considered one of the first-line therapies in elevated ICP. Head elevation seems to improve elevated ICP by increasing jugular venous outflow. However, head elevation also seems to decrease the arterial pressure reaching the brain, and CBF is observed to decrease as the head is raised from 0° to 45°. Thus, if the therapeutic priority is to maintain the highest possible CBF (as in hypotension), then supine positioning is best. In conditions where ICP is elevated and the goal is to optimize CPP, the ICP may be reduced with head elevation. Because of concurrent decreases in both ICP and CBF, CPP remains stable from 0° to 30°, but then begins to fall at 45°. Additionally, ICP may begin to increase at further head elevations of 60°.[54] Thus, positioning at 30° seems to provide optimum balance between ICP reduction and CPP preservation.[55] More moderate head elevation of 10° also appears to benefit ICP during craniotomy.[56]

Beyond elevation of the head of the bed, care should be taken to avoid rotation or flexion of the neck, as this may also limit venous outflow. Likewise, excessive taping or braces may lead to unnecessary jugular compression. Jugular vein thrombosis should be considered and ruled out in cases of neck trauma.[57] Rarely, placement of an internal jugular venous catheter can result in iatrogenic thrombosis and secondary elevations in ICP.[58] For this reason, we generally avoid cannulation of the internal jugular vein in cases of intracranial disease, and use either subclavian or femoral access sites.

Hyperosmolar Therapies

Principles of osmolar therapy

In a general sense, osmotherapy for elevated ICP can be thought of as the artificial induction of an osmolar force in order to reduce the volume of the intracranial contents.[59] The observation that osmolar gradients could lead to changes in the size of the brain parenchyma was first reported by Weed and McKibben at the Johns Hopkins Hospital in 1919.[60] They serendipitously discovered that intravenous injection of hypertonic saline led to a collapse of the thecal sac, whereas injection of free water caused marked brain swelling. At the same time, others observed clinical improvement in patients with elevated ICP with the administration of hypertonic glucose solutions.[61] Urea first debuted as a hyperosmolar therapy in 1927,[62] and was used for several decades before it was rejected in favor of other agents, given its significant adverse effects.[63] Use of sorbitol and glycerol as osmotherapeutics was first described in 1961,[64–65] although they were quickly supplanted by mannitol after it's introduction in 1962, as it offered several advantages over other hyperosmolar agents.[66,67] Specifically, it was easier to prepare and did not cause the gastrointestinal and hematologic side effects associated with urea; its use quickly became widespread. Despite its role in the discovery and development of osmolar therapies, hypertonic saline did not undergo further study during this time. There was a resurgence of interest in the 1980s, when hypertonic saline was used in the resuscitation of patients with hemorrhagic shock.[68–69] Hypertonic saline is now used with some frequency in the United States, particularly for refractory intracranial hypertension, although mannitol remains the mainstay of osmotherapy. Given their prevalent use, these two agents will be discussed in detail later.

Establishing an osmotic gradient, and hence therapeutic efficacy, depends on the solute's inability to cross the BBB. As discussed previously, this is quantified as the index of refraction (Table 6–3).[48] The osmotic force created by this gradient pulls water out of the brain parenchyma and decreases ICP, and a higher index of refraction leads to a steeper gradient. However, an intact BBB is critical to establishing and maintaining this gradient, and the BBB is frequently disrupted in conditions that cause elevated ICP. If the BBB is disturbed, even solutes with a high index of refraction are allowed to cross into the tissue. This would lead to a loss of the osmotic gradient and less efficacy. On the other hand, a disrupted BBB could more easily allow water to freely move out of the brain and into the intravascular space. The net effect of osmotherapy in regions of BBB disruption remains a matter of debate.[59]

Table 6–3 Index of Refraction for Major Osmolar Agents

Osmotic Agent	Index of Refraction
Mannitol	0.9
Hypertonic saline	1.0
Glycerol	0.48
Urea	0.59

One of the main problems recognized with the use of urea (and subsequently other osmotic agents) was that of rebound elevation of ICP after withdrawal of therapy.[70] Compounds with a lower reflection coefficient equilibrate more quickly across the BBB. When these agents are withdrawn from the plasma, a reverse osmotic gradient may be created. This may lead to the net influx of water into the brain, exacerbating edema and ICP.[71] Therefore, agents with higher reflection coefficients have been proposed as less likely to cause rebound increases in ICP.[72] This phenomenon may be more likely in areas of BBB breakdown.[73] However, rebound elevations in ICP may more likely be the result of compensatory formation of ideogenic osmoles after the prolonged exposure to an exogenous osmotic agent.[74] In this case, the rapid correction of a hyperosmolar state may be the reason for rebound changes in ICP, rather than a reversed gradient of osmolar agent concentrations.

Mannitol

Mannitol is the most frequently used osmolar agent for the treatment of elevated ICP. Its main mechanism of action is that described previously—an osmotic gradient forces water out of the brain parenchyma and into the intravascular space. The change in brain water content with mannitol infusion can be observed in real-time in patients undergoing craniotomy,[75] or by serial CT scan.[76]

In addition to the osmotic reduction of ICP, mannitol may have other pleiotropic effects on ICP and CPP.[77] First, mannitol may have a significant hemodynamic effect by virtue of hemodilution and decreased blood viscosity.[78] It is thought that this effect may result in increased CPP, CBF, and improved oxygen delivery.[79] This is particularly true for patients with suboptimal CPP prior to treatment, as they seem to show the largest decrease in ICP and benefit most from mannitol therapy.[80] The potential role of hemodilution in elevated ICP underscores the importance of careful fluid management and the avoidance of hemocon-centration in these patients.[59]

Mannitol is also a well-known diuretic, a property that may contribute to its ability to lower ICP. By reducing plasma volume, diuresis lowers the central venous pressure and improves jugular venous outflow. This is supported by the observation that administration of furosemide with mannitol prolongs ICP reduction.[81] However, the dangers of diuresis

outweigh the potential benefits. Specifically, diuresis worsens ischemia, and may lead to nephrotoxicity. In children with severe head injury, mannitol use has been independently associated with longer length of stay,[82] an effect that may relate to fluid shifts. Therefore, urine output should be replaced with intravenous fluids when mannitol is used. Beyond these mechanisms, mannitol may also improve ICP by decreasing the rate of formation of CSF,[83] and increase the rate of resorption.[84] Finally, mannitol appears to act as a free radical scavenger,[85] which may be neuroprotective.

The pharmacokinetics of mannitol in some ways make it the optimal osmotherapy. Mannitol is not metabolized and is eliminated by the kidneys according to first order kinetics. The half-life is approximately two to four hours, and depends on the glomerular filtration rate.[86] With a reflection coefficient of 0.9, a small but measurable amount of mannitol does cross into the brain parenchyma with each administration.[73] The half-life for elimination from the CSF is approximately 18 hours, but is highly variable.[87] Accumulation of mannitol can be seen in normal and injured brain tissue after repeated doses.[73] This accumulation may contribute to decreased efficacy after repeated administration, and is one potential reason for the rebound phenomenon. Given a serum half-life of two to four hours and CSF half-life of nearly 18 hours, some advocate a dosing interval of 12 hours (longer with renal failure) to prevent accumulation.[77]

Mannitol is usually administered intravenously, at a dose of 0.25–1 g/kg, over 15 to 30 minutes. Given the concern for accumulation, mannitol is frequently administered in boluses every 6–12 hours as needed.[77] However, some practitioners use smaller, repeated doses in an effort to maintain a sustained osmolar gradient. In this case serum osmolality should be maintained at 300–310 mOsm, and osmolality above 320 mOsm should be avoided.[26] This type of sustained mannitol therapy may also have some utility in cases when blood flow through the microcirculation is of particular concern, given mannitol's effect on blood viscosity.[59] The appropriate dose of mannitol may, in part, depend on the clinical condition. A recent trial showed that outcomes in severe head injury are improved with high-dose mannitol (1.4 g/kg) compared to standard dosing (0.7g/kg);[88] a finding further supported by a subsequent meta-analysis.[89]

The diuresis caused by mannitol infusion is significant—the volume of a single dose can elicit a diuresis five times greater in volume.[59] In other words, one liter of output can be expected for every 200 cc of mannitol solution infused. Fluid status therefore needs to be strictly managed in the patient receiving mannitol. Additionally, mannitol causes net loss of free water, which can result in significant electrolyte disturbances. Frequent monitoring and repletion of electrolytes is essential. If frequent or continuous infusions are used, serum osmolality must also be monitored regularly and kept below 320 mOsm to avoid nephrotoxicity.[77]

Mannitol has been shown to reverse acute transtentorial herniation,[25] and to improve outcomes in patients with severe traumatic head injury.[89] Many consider it to be one of the first-line treatments for acutely elevated ICP,[47] although it is certainly not without risks and it may be associated with longer length of stay.[82] When used as a bolus of 0.5–1.0 g/kg, it can rapidly reduce ICP and improve CBF.[59] Despite some disagreement as to whether it is more beneficial as a continuous infusion, most agree that intermittent bolus dosing is preferred.[26] When mannitol is used, strict fluid and electrolyte management is mandatory.

Hypertonic saline

Hypertonic saline (HTS) was one of the osmolar agents first described by Weed and McKibben in 1919.[60] Interest in clinical use of HTS did not arise until the 1990s, after it was studied for use in the rapid resuscitation of hemorrhagic shock.[90] Administration of small volumes of hypertonic saline establishes an osmotic force to draw fluid into the intravascular space, and can work as well as larger amounts of isotonic fluid administration in volume resuscitation. This osmotic dehydration of tissues is nonspecific and takes place in all organs, including the brain. The beneficial effect of HTS on ICP was first noted in trauma patients suffering both hemorrhagic shock and brain injury.[91] Since then, a number of animal studies and clinical trials have explored the role of HTS in the management of patients with elevated ICP,[92] and have even directly compared it to mannitol.[93]

The primary mechanism of action of HTS seems to be identical to that of mannitol. Namely, the increased osmolality of the serum causes water to flow out of the brain and into the intravascular space, reducing edema.[94] With a reflection coefficient of 1.0, sodium chloride is an ideal osmotic agent (assuming an intact BBB). Also like mannitol, HTS may have some other beneficial mechanisms of action. There is some evidence that HTS reduces blood viscosity, improving CBF and oxygen delivery.[95,96] Brain perfusion can be particularly important in cases of subarachnoid hemorrhage (SAH), when symptomatic vasospasm can lead to infarction. In the context of poor grade SAH, HTS has been shown to increase CBF and reduce brain ischemia,[97] although this effect has not been consistent.[98] Interestingly, despite mannitol's hemodynamic effects, it has never been formally studied in the context of SAH-induced vasospasm. In addition, HTS may diminish the inflammatory response associated with brain injury. Specifically, reduced leukocyte adhesion and diapedesis was observed after HTS administration in a single animal study.[99] And like mannitol, HTS may have beneficial (but transient) effects on cardiac output and CSF resorption.[92]

The cardiovascular effects of an HTS bolus last between 15 and 75 minutes in most animal studies,[100] although these effects may be closer to three hours in humans.[97] Hypertonic saline also causes a significant reduction of ICP in animals with cryogenic brain injury, which lasts for at least two hours after a single injection.[101] Human time-course data are limited, but it seems that single boluses of HTS reduce ICP for approximately two hours as well.[102] The effect on ICP can be prolonged with a continuous infusion of HTS after initial bolus. This method has been shown to be more effective in improving systemic hemodynamics and ICP in animal models.[103,104] In humans, repetitive doses or continuous infusions can reduce ICP in less than 20 minutes.[105] This effect can be maintained for at least 12 hours, but seems to dissipate by 72 hours.[106] Thus a continuous infusion of up to 72 hours may prolong the beneficial effects of HTS, including reduced ICP and improved hemodynamics. However, rebound ICP is always a concern with the prolonged administration of a hyperosmolar agent. Hypertonic saline is theoretically free from a rebound effect due to accumulation in the brain parenchyma, given its reflection coefficient of 1.0. But the BBB is likely dysfunctional in brain injury, and furthermore the rebound increase in ICP after prolonged exposure to hyperosmolar agents may be from the generation of ideogenic osmoles.[59] In practice, HTS does occasionally display a rebound phenomenon,[107] although the rate of serum sodium correction may be a more important factor.[108] An experimental comparison to mannitol in this regard is as yet unavailable.

A number of studies have compared HTS to mannitol. In general, similar effects on ICP have been observed.[109,110] However, the time course of ICP reduction after a single bolus may differ. Mannitol's effect may be slightly longer,[111] but the onset of action may be slightly quicker with HTS.[112] Additionally, HTS and mannitol may act at different sites. In one animal study using a cryogenic injury model, mannitol induced lower water content on the lesioned side of the brain, whereas HTS was associated with reduced water content on the non-lesioned side.[111] Likewise in an animal model of stroke, HTS caused a decrease of water content in the normal hemisphere and an increase of water content in the infarcted hemisphere, suggesting a deleterious effect of HTS in this situation.[113] In contrast, HTS seemed to prevail over mannitol in terms of ICP reduction, water content within the lesion, and CPP improvement, in an animal model of intracerebral hemorrhage.[114] These findings imply that the choice of osmolar therapies may be dictated by the etiology of brain injury.

The use of HTS has been studied in a variety of clinical contexts. In traumatic brain injury, HTS has been shown to improve ICP and midline shift,[106] but may be deleterious if administered for prolonged periods.[114] Furthermore, HTS seems superior to lactated ringer's solution in improving outcomes in pediatric head trauma.[115] When compared to mannitol, the use of HTS in traumatic injury may lead to more stable ICP and require fewer interventions, although there is no difference in outcomes.[93] Likewise, ICP may be more reliably controlled with HTS compared to mannitol in ischemic stroke;[112] but there remains the concern for worsening the edema in the area of the lesion.[113] This issue has not yet been addressed in humans. Also as described previously, the beneficial effect of HTS may have a role in the management of SAH-associated vasospasm,[97] although mannitol has never been studied in this scenario.

The optimal dosing of HTS is unknown. A variety of concentrations exist, from 0.9% to 23.4% saline solutions. Typically lower concentrations, such as 2% or 3%, are utilized when a continuous infusion and stable elevation of serum osmolality are desired. In this case, a serum sodium level of 145–155 mEq/1 is often targeted, which corresponds roughly to osmolality of 300–320 mOsm/1. Serum sodium levels should be checked at least every six hours. This type of infusion should probably not be continued beyond 72 hours if possible.[106] Particular caution should be used during withdrawal of HTS, as rebound hyponatremia can result in potentially catastrophic exacerbation of brain edema.[108] Occasionally, refractory ICP elevation may emergently be treated with a bolus of 23.4% saline.[116] Experience at our institution suggests that a 23.4% saline bolus, or a hypertonic bullet, can occasionally reverse herniation, and improve ICP and CPP for several hours while more definitive therapies can be considered (M. A. Koenig, et al, unpublished data, November 2006).

While HTS has a number of benefits, and even potential advantages over mannitol, it is not without risks. Most notably, infusion of large quantities of sodium chloride can cause a hyperchloremic metabolic acidosis. Therefore, a mixture of sodium chloride and sodium acetate is often used, particularly in the case of continuous infusions.[106] Similarly, HTS can precipitate hypokalemia and hypocalcemia, which is easily addressed with frequent monitoring and repletion. Volume expansion is expected with administration of hypertonic solutions, and the physician should remain vigilant for signs of fluid overload. Solutions greater than 2% saline often cause a phlebitis, and therefore a central venous catheter must be employed for their administration. Very large volumes of HTS can potentially cause coagulopathy, although not within the dose range used in practice.[117] There is also a theoretical concern that HTS may induce central pontine myelinolysis (CPM), a syndrome associated with the overly rapid correction of hyponatremia. Fortunately, this has never been described with HTS, and a recent study of 77 patients revealed no cases of CPM by MRI performed after administration of 23.4% saline (M. A. Koenig, et al, unpublished data, November 2006).

Corticosteroids

Inflammation is thought to play a role in almost every mechanism of brain injury, including ischemia, hemorrhage, infection, trauma, and neoplasia.[118] It is also well-established that inflammation in the brain causes edema, which in turn can elevate ICP.[119] The glucocorticoids have a multitude of physiologic effects in addition to their anti-inflammatory properties. Given these effects, it has been postulated that glucocorticoids are neuroprotective; by reducing inflammation and restoring the BBB, vascular permeability decreases and edema is improved.[120,121] This implies that use of glucocorticoids for the treatment of brain edema should be limited to cases of BBB breakdown and vasogenic edema. Regardless of the mechanism, and whether cytotoxic or vasogenic edema predominates, glucocorticoids have been studied in a wide variety of neurologic diseases associated with increased ICP.

The main role of glucocorticoids in treating elevated ICP is with brain tumors. In this case, the edema is almost entirely vasogenic and extracellular. Rapid improvement of the radiographic correlates of this edema can be seen within 48–72 hours after administration of dexamethasone.[122] Clinically, improvement of symptoms can generally be seen within 24–72 hours of glucocorticoid initiation in about 75% of patients.[123] Interestingly, the most dramatic improvements are usually in those symptoms associated with globally elevated ICP, including headache and altered mental status, suggesting that glucocorticoids may indeed have a substantial effect on ICP. The effective dose of dexamethasone is usually 2–4 mg twice daily, although higher doses should be considered if signs of elevated ICP are present.[124] Specifically, an initial dose of 10 mg delivered intravenously, followed by 4 mg every 6 hours, may be used for brief periods in the setting of symptomatic increased ICP.[125] Glucocorticoids can usually be weaned within two weeks, although perhaps 25% of patients with brain tumors will require long-term treatment.[123]

Glucocorticoids have a definitive role in the treatment of bacterial meningitis,[126,127] although the therapeutic mechanism likely has little to do with ICP in this setting. Brain abscess, on the other hand, represents a CNS infection that can potentially be complicated by significant mass-effect and elevated ICP. In severe brain abscesses, particularly with evidence of surrounding vasogenic edema, glucocorticoid therapy may be considered as a short-term treatment for elevated ICP,[118] although this treatment has not been systematically studied. One should also keep in mind that glucocorticoids are thought to repair the BBB, which may limit the penetrance of antibiotics into the CNS.[128]

Traumatic brain injury is one of the most important and common causes of elevated ICP. The role of glucocorticoids in treating the brain edema associated with traumatic injury has been studied since 1976,[129] and has been the subject of several comprehensive reviews.[26,130] While some of the early data were supportive of the role of glucocorticoids in head trauma,[129] most of the subsequent, larger trials have shown no benefit,[130] and none have shown a beneficial effect on ICP. Most recently, a trial of over 10000 patients with traumatic brain injury was stopped early after finding a significantly increased risk of death associated with glucocorticoid administration compared to placebo.[131] At this point, the recommendation against the use of glucocorticoids in severe head trauma[26] is supported by substantial evidence from clinical trials.

Glucocorticoids have also been studied in for their role in reducing brain edema secondary to stroke. In ischemic stroke, cytotoxic edema initially predominates, but vasogenic edema tends to accumulate over 48–72 hours as the lesion evolves. This has led to the hypothesis that glucocorticoids might be useful in reducing edema, which is partially supported by data from animal studies.[118] However, data from clinical trials do not support this view. A recent systematic review concluded that glucocorticoids do not affect outcome or mortality in ischemic stroke, and may be associated with more adverse effects.[132] Data for hemorrhagic stroke (intracerebral hemorrhage) are more limited, but no difference in outcome has been observed in randomized trials,[133] and there is more suggestion of serious adverse events associated with glucocorticoid use.[134]

General anesthesia

The effect of barbiturates on ICP was first described in 1937.[135] The barbiturates potentiate and mimic the effects of GABA, predominantly at the GABA-A receptor complex, and induce cortical inhibition. It is thought that barbiturates decrease brain metabolism, which reduces the demand for oxygen, and CBF is then decreased by autoregulatory mechanisms. The decrease in CBF results from a constriction of cerebral blood vessels and leads to reduction in cerebral blood volume and ICP.[136,137] By first reducing the brain's metabolic demand, it is thought that barbiturates may help to optimize oxygenation in cases of inadequate CPP.

Barbiturates have been evaluated as treatment for elevated ICP in several settings, including hemispheric stroke[138] and liver failure,[139] but are best studied for their use in brain trauma.[26] Because of serious side effects, use is usually limited to the most severe cases of brain injury and refractory ICP. This is an important role, however, because as many as 15% of patients with head trauma will exhibit refractory elevations in ICP, which is associated with an 84%–100% mortality rate.[26] In this context, pentobarbital was evaluated in a randomized controlled trial of refractory ICP in head trauma patients with a Glasgow Coma Scale between 3 and 9.[140] Intracranial pressure was controlled twice as frequently with the use of pentobarbital, and a significant reduction in the mortality rate from 83% to 8% was observed if the ICP responded to barbiturate treatment. This effect has been corroborated by others,[141] and serves as the foundation for the BTF guideline that high-dose barbiturate therapy should be considered in cases of elevated ICP refractory to maximal medical and surgical therapy.[26] On the other hand, barbiturates should not be used as ICP prophylaxis; the early use of barbiturates may lead to serious side effects[142] and worsen outcomes.[143] The use of barbiturates is also not warranted in treating elevated ICP associated with large strokes,[138] but may have some role in patients with hepatic failure.[139]

In cases of severely elevated ICP refractory to other therapies, pentobarbital is the most frequently used barbiturate. Pentobarbital is generally administered as an initial bolus of 10 mg/kg over 30 minutes, followed by a maintenance infusion at 1.0 mg/kg per hour. Serum levels in the range of 3 mg/dL are generally effective at lowering ICP, and levels should probably be monitored frequently as pentobarbital often induces its own hepatic metabolism. However, the dosing of pentobarbital should be titrated to a burst-suppression pattern on continuous electroencephalographic (EEG) monitoring rather than serum levels. Other barbiturates can also be used for the management of refractory ICP, however, the long halflife of phenobarbital and difficulty in titrating thiopental have limited their use compared to pentobarbital.[144]

The disadvantages of the barbiturates are significant. Patients are often in pharmacologic coma for prolonged periods (up to one week or more), during which time neurologic status cannot be evaluated by exam. Barbiturates also suppress the autonomic nervous system. They induce a profound respiratory depression, and hence all patients must be intubated and mechanically ventilated prior to initiation of therapy. Mucocilliary function in the respiratory tract is also suppressed, greatly increasing risk of pneumonia. Barbiturates can also cause severe hypotension requiring continuous monitoring, and often necessitate the use of pressors. Patients are frequently poikilothermic, and fever frequently does not manifest in infection. This is particularly relevant as highdose barbiturates can lead to immunosuppression, and thus surveillance for infection must be undertaken.[145]

In addition to the barbiturates, propofol is sometimes used for the control of refractory ICP. The mechanism of action of propofol is probably the same as the barbiturates; decreased cerebral metabolism leads to a reduction in CBF and hence ICP.[146] Propofol has not been studied as extensively as barbiturates for the reduction of refractory ICP, but limited data do suggest that it is effective in head trauma[147] and may be equally efficacious.[148] Furthermore, the clinical experience with its use as a sedative is considerable.[144] The disadvantages of propofol are largely similar to those of the barbiturates, and include hypotension, respiratory depression, immunosuppression, and obscuration of the neurologic exam. The most serious, but rarest, adverse reaction to propofol has been called the propofol infusion syndrome, which is characterized by cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure.[149] This syndrome tends to occur more often in children than adults, and may be potentiated by concurrent use of corticosteroids, vasopressors, or the prolonged use of propofol in high doses.[150] The high lipid content of emulsified propofol can also cause

hypertriglyceridemia, which may rarely lead to pancreatitis.[151] The major advantage of propofol is its rapid clearance and neurologic recovery once discontinued.[150] If used for the management of ICP, continuous EEG monitoring should be employed to titrate the propofol dose to a burst-suppression pattern.

Other therapies

Hypothermia has recently been shown to improve neurologic outcome after cardiac arrest.[152,153] The mechanism is not precisely known, but may involve decreased cerebral metabolism, blunting of the ischemic loss of ion gradients, reduction in free radicals, and anti-inflammatory effects.[154] While hypothermia is clearly neuroprotective in a number of animal models of brain injury,[155] its clinical utility in settings other than cardiac arrest has yet to be substantiated.[156] In hemispheric strokes, hypothermia causes an initial decrease in ICP followed by a rebound ICP increase,[34] and its effect on outcomes is unknown.[157] Therapeutic hypothermia has been shown to reduce ICP and improve CPP in the setting of severe head trauma.[158] In patients with severe traumatic brain injury and elevated ICP refractory to barbiturate coma, hypothermia can significantly improve outcomes compared to normothermia,[159] although these results are inconsistent.[160] When utilized in cardiac arrest, therapeutic hypothermia usually consists of lowering core temperature to 32°–34°C for a period of 12–24 hours.[161] The optimal duration of hypothermia in brain trauma is unknown, but periods of 72 hours[158] or more[159] have been used with some success. Longer duration, however, may increase the likelihood of adverse events. Specifically, hypothermia seems to predispose to hyperglycemia;[152] electrolyte disturbances;[162] infection;[160] and cardiovascular changes including bradycardia, increased systemic vascular resistance, and an altered electrocardiogram.[152] Hypothermia may interfere with the coagulation cascade, as suggested by increased bleeding and clotting times with cooler temperatures.[163] Thus, while clearly beneficial for comatose patients after cardiac arrest, the role of therapeutic hypothermia in elevated ICP is restricted to the most refractory patients, given its significant potential for harm and unproven efficacy.

Tromethamine, or THAM, is a buffer that can cross the BBB and reduce brain acidosis and ICP in some animal models of brain injury.[164] The single clinical trial of THAM in severe head injury did show a significant reduction in ICP compared to control.[165] However, all 149 patients in this trial were treated with prophylactic hyperventilation for five days, a practice that should probably be avoided.[26] It may be that the ICP-reducing effect of THAM was the result of an interaction with prolonged hyperventilation. Furthermore, there was no difference in outcomes between the treatment and control groups, although there was a nonsignificant trend toward worse outcomes associated with THAM. Thus, the current evidence does not support a role for THAM in the treatment of elevated ICP, and its use should be restricted to clinical trials.

Acetazolamide is a powerful carbonic anhydrase inhibitor, and can decrease the rate of CSF production by more than 50% in the choroid plexus.[166] By this mechanism, it has been postulated that acetazolamide could be used to treat elevated ICP, and is used frequently for this purpose in idiopathic intracranial hypertension (pseudotumor cerebri).[28] However, a controlled trial evaluating this usage has not yet been done, and the limited clinical data available suggest that it may not be helpful.[167] Nonetheless, acetazolamide, and other carbonic anhydrase inhibitors such as topiramate, remain in widespread clinical use for chronic disorders of elevated ICP.[168]

Indomethacin is a nonselective cyclo-oxygenase inhibitor that seems to induce cerebral vasoconstriction, decreasing CBF and hence ICP.[169] In patients with brain trauma, it has been shown to rapidly reduce ICP,[170] and may improve CPP.[171] Likewise in patients with cerebral tumors, indomethacin has been shown to significantly lower ICP rapidly after its administration.[172] However, this study also revealed a significant decrease in CBF, which raises the concern for potential cerebral ischemia. Animal studies have yielded mixed results, varying from ischemia to neuroprotection associated with indomethacin.[169] Clinical studies have revealed significant signs of critically low CBF associated with indomethacin use, including increased brain lactate,[172] although indomethacin does not seem to induce ischemic changes on MRI.[173] Given the significant concern for cerebral ischemia and the absence of randomized, controlled trials, the current use of indomethacin for treatment of elevated ICP is purely experimental.

Aside from the specific therapies described previously, others propose a volume-targeted therapy that focuses more on improving ICP and less on CPP.[174] The four main tenets of this approach (the Lund Concept) are: reduction of stress by sedation; reduction of hydrostatic pressure by controlling MAP; maintaining normal colloid osmotic pressure with the liberal use of transfusions; and the reduction of cerebral blood volume using low-dose barbiturates and DHE, a potent cerebral vasoconstrictor.[175] Additionally, practitioners of this therapy discourage the use of hyperosmolar agents, head elevation beyond 20°, the use of vasopressors, and the use of hyperventilation for more than two minutes.[174] While volume-targeted therapy appears to have improved outcome compared to historical controls,[176] its efficacy remains to be proven in a randomized, controlled trial. Nonetheless, some of its fundamental aspects, including close attention to volume status and avoidance of stress, are key elements in the practice of critical care medicine.

Surgical interventions

Despite the plethora and proven efficacy of the medical therapies described previously, surgical interventions are more often the definitive treatment. However, these treatments are also associated with significant risks, and are more often tailored to the individual patient. Particular diseases may be more amenable to surgical intervention. For example acute obstructive hydrocephalus is optimally treated with CSF diversion. Likewise many tumors, while they may be treated in the short term with glucocorticoids, are definitively treated with resection. In contrast, the evacuation of a space-occupying hematoma after intracerebral hemorrhage may not benefit outcome.[177] Therefore, the decision to proceed with craniotomy depends on careful consideration, on a cases-by-case basis, of pathological condition and the relative risks and benefits of treatment options. Ultimately, many patients benefit from a combination of medical and surgical interventions.

CSF Diversion and Drainage

As described previously, the EVD offers ICP monitoring and CSF drainage capabilities. In the case of acute hydrocephalus, CSF diversion is the most appropriate therapy. Once the cause is treated and normal CSF dynamics are restored, the EVD can be removed. The restoration of normal CSF resorption is roughly gauged by the drainage rate. If CSF is allowed to drain only when the pressure is above 15 cm H_2O, a normal drainage volume should be less than 100 cc per day. Greater values are suggestive of abnormal CSF flow or resorption, and are an indication for continued therapy. Likewise when volumes less than 100 cc per day are associated with normal ICP for 1–2 days, the EVD can safely be discontinued.[145]

Chronic forms of elevated ICP or hydrocephalus often require long-term CSF diversion. The diagnosis of NPH is often made with ICP monitoring via lumbar drain.[29] If a response to CSF drainage is observed, these patients usually undergo shunt surgery for long-term CSF diversion.[31] Patients with idiopathic intracranial hypertension also suffer from chronically elevated ICP, and frequently require surgical intervention. Cerebrospinal fluid diversion, with lumboperitoneal or ventriculoperitoneal shunts, is standard surgical treatment for these patients,[28] although optic nerve fenestration may represent an alternative therapy.[178] Shunts are also associated with a number of complications including infection, obstruction, and headache.[179] Finally, obstructive hydrocephalus may also be treated with endoscopic third ventriculostomy, which allows the intraventricular CSF to flow directly into the subarachnoid space of a basal cranial cistern.[180]

Decompressive Hemicraniectomy

Massive strokes, particularly in the middle cerebral artery distribution, can cause considerable cerebral edema and elevated ICP. These strokes can frequently lead to cerebral herniation and death.[34] Decompressive hemicraniectomy has been proposed as a way to relieve the edema by creating a large cranial bone flap and expanding the dura with a dural patch. Unfortunately, no controlled trial of this therapy for hemispheric stroke has yet been published, although several are underway.[157,181] In uncontrolled trials, hemicraniectomy resulted in death or severe disability in 58% of patients with hemispheric infarcts,[182] which may compare favorably to historical controls.[34] Notably, patients less than 50 years of age seemed to derive greater benefit from hemicraniectomy.[182] Decompressive craniectomy has also been the subject of uncontrolled study in brain trauma.[183] In the absence of data from controlled trials, hemicraniectomy must be regarded as an experimental therapy for elevated ICP, although its usage depends on experience and setting.[184]

Removal of Mass Lesions

The most direct treatment of a space-occupying lesion causing elevated ICP is resection. For example, the rapid accumulation of blood in the form of either an epidural or subdural hematoma has the capacity to cause significantly raised ICP. In these instances, the evacuation of the hematoma can lead to dramatic improvements in clinical status and outcome.[185,186] Likewise, cerebellar hemorrhage (or infarction) can lead to acute brainstem compression, and is frequently treated surgically with evacuation or decompression.[187] The role of evacuation in deeper, intracerebral hemorrhages is less clear. A recent multicenter, randomized trial failed to demonstrate the utility of hematoma evacuation in ICH.[177] Brain abscesses and tumors can also produce significant mass-effect and elevated ICP, but their presentation and courses are protean, and decisions regarding surgical interventions must be made on an individual basis.

Conclusion

Elevated ICP can result from a multitude of diseases, and is most commonly encountered in the critical care setting as a neurologic emergency. Its rapid recognition and treatment depend on an understanding of its pathophysiology, and can be life saving. Intracranial pressure is related to intracranial elastance, the BBB, and CBF. Elevated ICP can lead to poor cerebral perfusion and ischemia, brain herniation, and death. Intracranial pressure is a frequently monitored physiologic variable in critical care, and knowledge of its waveform can aid recognition of poor intracranial compliance. After raised ICP is diagnosed, there are a number of treatment options. Hyperventilation offers a short-term strategy for lowering ICP, but may cause ischemia due to vasoconstriction. Mannitol and hypertonic saline may be used to decrease brain water content and hence ICP and may also improve cerebral blood flow dynamics. However, these osmolar therapies may be associated with their own risks, including a potential rebound effect. Glucocorticoids may be used to treat elevated ICP associated with vasogenic brain edema. Pharmacologically induced coma may be considered in cases of elevated ICP refractory to other therapies. There are also a number of experimental therapies for elevated ICP, including other pharmacotherapeutics, volume-targeted therapy, and hypothermia. Surgery offers definitive treatment, and should always be considered in cases of elevated ICP. The surgical options include CSF drainage, hemicraniectomy, and mass resection. The approach to each patient with elevated ICP can, and should, be individualized based on pathology and available treatment options.

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Cognitive disorders including dementia, mild cognitive impairment associated with aging, and deficits in attention and memory following traumatic brain injury, are common causes of disability. In 2007 it was estimated that more than five million people in the United States had Alzheimer's disease (AD), including more than 12% of those over age 65 and more than 42% of those over age 85.[1] As longevity increases, the number of individuals in the United States with AD is expected to expand to more than 13 million by 2050 if no intervention is found.[2] The Center for Disease Control estimates that an additional five million Americans suffer from long-term cognitive and behavioral impairments associated with traumatic brain injury.[3] Acetylcholinesterase inhibitors, which raise synaptic levels of acetylcholine, and memantine, a blocker of the N-methyl-D-aspartate (NMDA) type glutamate receptor, have been shown to improve cognitive function and activities of daily living in patients with AD and are widely prescribed.[4] These strategies are also being explored for use in other cognitive disorders. On the horizon are approaches directed at interrupting the formation of amyloid-containing plaques and neurofribrillary tangles associated with AD.[5]

Dementia and related disorders

Alzheimer's Disease

Dementia is a progressive, pervasive disorder characterized by loss of memory and intellectual abilities affecting social or occupational functioning. Alzheimer's disease accounts for more than half of the cases of dementia in older persons and accounts for about half of admissions to nursing homes in the United States.[6] According to the National Institute of Neurological Disease and Stroke-Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) criteria, the diagnosis of probable AD is appropriate when a clinical and neuropsychological examination establishes progressive deficits in two or more areas of cognition, including memory, with onset between ages 40 and 90 in the absence of delirium or another brain disease that could produce dementia (Table 7–1). The American Psychiatric Association *Diagnostic and Statistical Manual IV-TR* criteria for AD are similar, but specify deficits in memory and executive function as well as either aphasia, apraxia, or agnosia, as well as a significant impairment in social or occupational functioning.[6] Both criteria depend on the exclusion of other conditions including depression or another psychiatric disease, sedative drugs or toxins, alcoholism, vitamin deficiency, hypothyroidism, other metabolic/ genetic disorders, subdural hematoma, brain tumor, or hydrocephalus.

Table 7–1 Definitions of Alzheimer's Disease
DSM-IV-TR Development of multiple cognitive deficits including memory deficits and one of the following: aphasia, apraxia, or agnosia Cognitive deficits reflect a decline from previous functioning and impair social or occupational functioning There is gradual onset and continuing decline Not due to other disease or substance-induced condition Not better accounted for by another psychiatric disorder
NINDS-ADRDA *Definite Alzheimer's disease:* meets criteria for probable Alzheimer's disease and has evidence of disorder on autopsy or brain biopsy *Probable Alzheimer's disease:* Dementia established by clinical and neuropsychological examination and involves: a. progressive deficits in two or more areas of cognition, including memory, b. onset between ages 40–90, and c. absence of systemic or other brain diseases capable of producing a dementia syndrome, including delirium. *Possible Alzheimer's disease:* a dementia syndrome with an atypical onset, presentation, or progression and without a known etiology; any comorbid diseases capable of producing dementia are not believed to be the cause *Unlikely Alzheimer's disease:* a dementia syndrome with any of the following: sudden onset, focal neurologic signs or gait disturbance early in the course of the illness

A definite diagnosis of AD is established when characteristic histopathologic evidence is obtained from autopsy or a brain biopsy in a patient with probable AD. Pathologic signs include amyloid plaques, neurofibrillary tangles associated with neuronal loss and atrophy of the mesial temporal lobe including the hippocampus and entorhinal cortex.[7,8] Plaques are composed of extracellular deposits of fibrillar and amorphous aggregates of β-amyloid peptide (Aβ), while neurofibrillary tangles are made up of aggregates of the microtubule-associated protein tau, which has been hyperphosphorylated and oxidized.[8–10] Diffuse deposits of Aβ are also present, as well as evidence of inflammation including reactive gliosis, microglial activation, and inflammatory proteins and complement activation.[11] Magnetic resonance imaging (MRI) evidence of mesial temporal and hippocampal atrophy with cortical atrophy and ventricular enlargement supports the diagnosis of AD but is not definitive.[12] Glucose hypometabolism measured with positron emission tomography (PET) is also prominent in the cerebral cortex of patients with AD, especially in the frontal, parietal, and temporal lobes of patients with early onset disease.[13] The frontal cortex is less affected in patients who develop AD later in life.[14] Impaired glucose metabolism probably reflects disrupted function of synapses in AD as well as reductions in the activity of oxidative enzymes associated with mitochondria.[15,16]

Mild Cognitive Impairment

Many elderly patients present with subjective memory complaints and score below age-adjusted standards on memory tests but are not impaired in activities of daily living or do not have impairment in two or more cognitive domains. When investigation fails to find structural, toxic, metabolic, or psychiatric causes, they are usually given a diagnosis of mild cognitive impairment (MCI).[17] Longitudinal studies indicate that approximately 10% of these patients per year will meet criteria for AD and that the majority will eventually fulfill clinical and pathologic criteria for this diagnosis. For many patients, MCI reflects an intermediate state between normal aging and AD, which might be amenable to early intervention with disease modifying therapies in the future.[18] Smaller hippocampal and entorhinal cortex volumes measured on MRI combined with age and cognitive variables help to predict conversion from MCI to AD.[19] Early studies suggest that PET ligands that detect the accumulation of amorphous aggregates of amyloid in senile plaques and tau protein in neurofibrillary tangles might be used to diagnose early AD in patients with MCI.[20] However, at this time they are not specific for the disorder and should be interpreted cautiously. Measurement of Aβ and tau proteins in cerebrospinal fluid is also being examined as a way to diagnosis early AD in nondemented older adults with MCI, but has not yet been established as a diagnostic test.[21]

Vascular Cognitive Impairment

Vascular dementia, considered to be part of the spectrum of vascular cognitive impairment (VCI), is the second most common form of age-related dementia.[22] Vascular cognitive impairment includes dementia following a major cortical stroke or smaller strategically placed vascular lesions in the basal ganglia or thalamus. The cognitive profile of VCI includes more prominent psychomotor slowing and executive dysfunction in contrast to the memory and language disorders seen early in AD. However, diagnostic delineation of VCI remains challenging. The neuropathology of patients with VCI is heterogeneous and pure vascular dementia has been found in less than 10% of autopsied cases in some series.[23] Dementia occurs in one third of elderly individuals with stroke, and many of these patients also have AD with a mixed vascular-AD pathology. In one study of brain pathologies in community dwelling older persons, more than half of those with dementia had mixed brain pathologies including AD and cerebral infarctions.[24] Risk factors such as elevated blood lipids, hypertension, and elevated plasma homocysteine are common to patients with both vascular cognitive disorders and AD, and epidemiological studies suggest that these conditions constitute a continuum rather than distinct entities.[25] It has been proposed that hypoperfusion may contribute to AD pathology in some patients.[26] Postmortem brain tissue from patients with vascular dementia has been reported to have some neurochemical changes that resemble those in AD.[27] Vascular cognitive impairment is also found in patients with a variety of subcortical small vessel disorders, including age related white matter lesions associated with hypoxiaischemia and microinfarcts.[22] Genetic small vessel diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) also cause dementia in a small number of patients from age 40 to 60.[28] Sporadic or genetically based cerebral amyloid angiopathies are also rare causes of vascular dementia.[29]

Other Causes of Dementia

Although the majority of patients with dementia will fall into the AD, MCI, and VCI categories, there are many other potential causes (Table 7–2). These include normal pressure hydrocephalus (NPH), frontotemporal dementia, dementia with Lewy bodies, progressive supranuclear palsy, primary progressive aphasia, traumatic brain injury, and Huntington's disease, and endocrine disorders such as hypothyrodism and brain tumors (Table 7–2).[30–32] Infectious causes include human immunodeficiency (HIV) dementia, syphilis, progressive multifocal leukoencephalopathy, and prion diseases such as Creutzfeld-Jakob disease.[33] Parkinson's disease and multiple sclerosis can also cause dementia. Patients with Down syndrome often develop neuropathologic and cognitive changes consistent with AD as young adults,[34] and patients with Niemann-Pick type C and adult onset ceroid lipofuscinosis (Kufs disease) can develop dementia at relatively young ages.[35,36]

Table 7–2 Causes of Dementia

Causes of Dementia
Alzheimer's disease (AD)
Vascular cognitive impairment (VCI)
Normal pressure hydrocephalus (NPH)
Traumatic brain injury
Frontotemporal dementia
Dementia with Lewy bodies
Progressive supranuclear palsy
Primary progressive aphasia
HIV-associated dementia
Huntington's disease
Syphilis
Progressive multifocal leukoencephalopathy
Creutzfeld-Jakob disease
Parkinson's dementia
Multiple sclerosis
Down syndrome with AD pathology
Endocrine disorders (e.g., hypothyroidism)
Brain tumors Chronic hypoxemia Subdural hematoma
Pseudodementia from sedatives, drugs of abuse
Genetic storage diseases (e.g., Niemann-Pick C and Kuf's disease)

Cognitive Impairment from Drugs or Metabolic Disorders

Cognitive impairment from drugs prescribed for anxiety, insomnia, or behavioral disturbances is common in the elderly population and may be confused with dementia.[37] Benzodiazepines such as lorazepam commonly produce amnesia even in younger individuals when prescribed for procedures such as endoscopy or cancer chemotherapy.[38] Triazolam, a triazolobenzodiazepine hypnotic agent, has also been reported to produce episodes resembling transient global amnesia in certain individuals.[39] Experiments in young subjects indicate that benzodiazepines, which enhance the activity of γ-aminobutyric acid (GABA) receptor, disrupts attention, vigilance, and memory for information requiring processing effort, but access to knowledge already memorized remains intact. The sedative drug zolpidem also enhances the effects ofGABA receptors although not at the benzodiazepine site and it is not classified as a benzodiazepine.[40] Antipsychotic drugs can also produce cognitive impairment that simulates dementia in elderly individuals.[41] Hypoxemia, alcohol withdrawal, hypothyroidism, and other metabolic disorders are also important potentially t reatable causes of cognitive dysfunction, including delirium and amnesia.[42] Like drugs, their presence may exaggerate modest cognitive decline in older individuals and tip the balance toward confusion and total dependence on others.[43]

Pathogenesis of ad

Amyloid-β Peptide Accumulation

Altered processing of amyloid precursor protein (APP) resulting in the accumulation of Aβ in the brain is currently considered to be the most important initiating process in AD, and one that links together the other diverse synaptic and neurochemical pathologies (Figure **7–1**).[8,10] There is a general correlation between the amount of amyloid in the brains of patients with AD and severity of dementia but neuronal loss and the number of neurofibrillary tangles in the hippocampus are more strongly related to cognitive level.[44] Amyloid precursor protein is located on chromosome 21, and individuals with Down syndrome, who are trisomic for 21, accumulate Aβ and develop premature pathology of AD.[45] Mutant mice in which APP processing is disrupted and Aβ accumulates develop memory disturbances that parallel the appearance of the peptide, and they develop synaptic pathology that resembles that seen in AD.[46–48] In cell culture, Aβ has been shown to kill cultured neurons as well as disrupt energy homeostasis, membrane transporters including glutamate transporters, and electrophysiologic synaptic plasticity.[16,49] Amyloid-β has also been shown to induce oxidative stress when it accumulates in membranes of neurons and mitochondria, resulting in lipid peroxidation, excessive calcium entry, and generation of oxygen free radicals.[15] Amyloid-β oligomers have also been shown to bind to NMDA receptors, enhancing their function so that neurons are damaged through an excess of calcium fluxed through NMDA channels.[50] Excessive NMDA receptor activity has also been linked to hyperphosphoryltion of tau, which contributes to neurofibrillary tangles.[51] Additional evidence supporting the amyloid hypothesis for AD is provided by the observation that immunization of APP mutant mice with antibodies against Aβ resulted in clearance of the peptide as well as improvement in memory.[52,53]

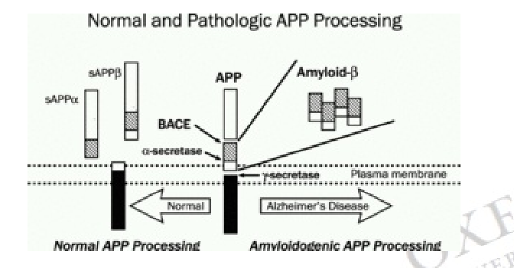




Figure 7–1.
Normal and pathologic APP processing. Amyloid precursor protein (APP) is a normal membrane-spanning protein that has roles in neuronal survival and plasticity. Cleavage of APP by α-secretase can lead to soluble proteins (sAPPa and sAPPβ) that have physiological funcions. However, cleavage by γ-secretase and BACE (β site of APP Cleavage Enzyme) leads to formation of amyloid-β, which is toxic.

The mechanism for accumulation of Aβ peptide in the vast majority of patients with sporadic AD is unclear, but familial forms of the disorder have provided insights into excessive production caused by defects in proteolytic enzymes that normally process APP (Figure **7–1**).[7] Amyloid precursor protein is an integral membrane-spanning protein that may have roles in neuronal survival and plasticity. Amyloid precursor protein can be cleaved at α-, β-, or γ-secretase sites, and sequential cleavage by BACE (β site of APP cleavage enzyme) and α-secretase yields fragments of APP that have physiological functions.[8,54] However, cleavage by BACE and γ-secretase leads to production of Aβ, which is toxic. Mutations that result in familial AD change the APP protein so that cleavage by BACE and γ-secretase is enhanced or change the presinilin gene to modify γ-secretase activity.[55] It is thought that other environmental or metabolic factors such as a high fat diet could modify APP processing through mechanisms such as oxidative stress. Cholesterol lowering statin drugs have been shown to decrease Aβ levels in APP mutant mice while high cholesterol levels may increase peptide accumulation, possibly by enhancing lipid peroxidation.[56] Apolipoprotein E phenotype may also increase the risk of AD by enhancing Aβ aggregation.[57] Oxidative stress related to

inflammation may also play a role as it has been shown that nonsteroidal antiinflammatory drugs may reduce the risk of AD if taken before the disorder begins.[58] An explanation for why these changes in APP processing target synapses and axons in AD may be that APP is normally transported within axons and its processing is regulated by synaptic activity. Neurons with long projections, such as the cholinergic system, or neurons with strong excitatory synaptic inputs, such as those in the hippocampus, might be more likely to accumulate Aβ.[8]

Involvement of Cholinergic Neurons

Neurons and synapses in the cerebral cortex are the major targets for AD, and the neurons that produce acetylcholine are among the earliest to be affected.[59,60] Enhancing the function of damaged cholinergic neurons is one of the major therapeutic strategies for treating AD.[61] Their role in memory was recognized because of the observation that muscarinic antagonist drugs such as scopalomine can impair memory when used in high doses for anesthesia. Drachman and Leavitt administered scopolamine to normal college students and compared the deficits it produced to the memory loss associated with aging.[62] Using tests of digit span, free recall for words, category retrieval, and the Wechsler Adult Intelligence scale, they found that administration of a high dose of scopolamine produced deficits that are quite similar to those seen in aged subjects. In contrast, the muscarinic agonist arecoline has also been shown to enhance serial learning in young human subjects and patients with AD.[63]

The cholinergic innervation of the cerebral cortex is derived predominantly from subcortical projections (Figure **7–2**).[64,65] Four cholinergic cell groups in the basal forebrain (the medial septum, the vertical and horizontal limb of the diagonal band of Broca, and nucleus basalis of Meynert) project axons into the hippocampus and cerebral cortex.[66,67] These cholinergic cell bodies have been grouped and named Ch1 through Ch4. Cholinergic cell bodies in the medial septal nucleus and the vertical limb of the diagonal band provide the major cholinergic innervation into the hippocampus, whereas those of the horizontal limb of the diagonal band provide cholinergic axons to olfactory structures.[67] The cerebral cortex receives the vast majority of its cholinergic input from the Ch4 region of the nucleus basalis. The majority of the cholinergic innervation to the cerebral cortex in primates comes from the basal forebrain projection, and the nerve fibers are distributed diffusely throughout cortical layers.[67]

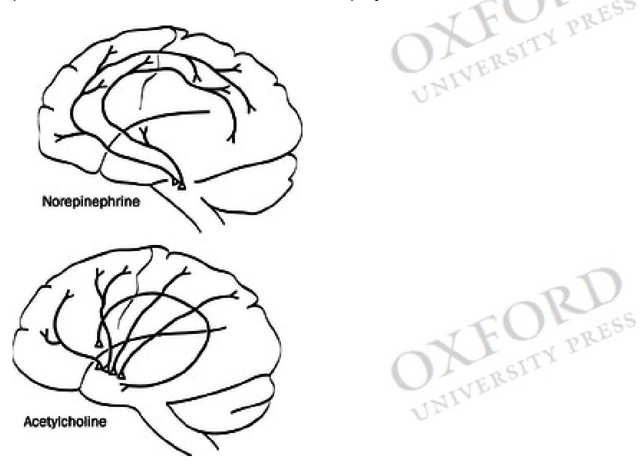




Figure 7–2.
Schematic distributions of two neurotransmitter systems that are affected in AD. Cell bodies for noradrenergic neurons that contain norepinephrine are located in the pons, and project axons upward and diffusely throughout the cerebral cortex (upper drawing). Norepinephrine is involved in attention, arousal and regulation of sleep. Most of the acetylcholine in the cerebral cortex is contained within axons of cholinergic neurons that originate in the nucleus basalis of Meynert in the basal forebrain (lower drawing). Cholinergic neurons are involved in memory formation and activity dependent plasticity of cerebral cortex, and they are among the earliest neurons to be affected by AD pathology.

The basal forebrain cholinergic projection appears to play a role in integrating cognitive, vegetative, and motivationally relevant information.[68] These basal forebrain nuclei receive substantial input from the hypothalamus and components of the limbic system.[67] In physiologic studies, electrical activity in the nucleus basalis has been shown to increase after monkeys are rewarded with juice for successful performance of a motor task.[68] Experiments in which the glutamate analogue neurotoxin ibotenic acid was used to damage the nucleus basalis of squirrel monkeys demonstrated that this lesion produced severe and enduring learning and memory deficits in several visual memory tasks.[69] Decker and colleagues demonstrated changes in high-affinity choline uptake into cholinergic nerve endings in the hippocampus and the cortex as a result of training on a spatial memory task.[70] These results suggest that the cholinergic pathways are activated by training that results in memory storage.

Function of the Cholinergic Synapse

The biochemical machinery of the cholinergic synapse, which is a major target for therapy in AD, is shown in Figure **7–3**. Acetylcholine is synthesized from acetylcoenzyme A (AcCoA) and choline by choline actyltransferase (ChAT).[71,72] The usual brain concentrations of choline and AcCoA are below those needed to saturate ChAT, and experimental elevation of brain choline or AcCoA can alter the rate of acetylcholine turnover.[73] Choline is able to pass easily across the blood brain barrier (BBB) via a facilitated diffusion system in the capillary endothelial cell. Brain choline concentrations tend to be higher than those in the plasma, possibly related to the fact that the brain neurons can synthesize choline by sequential methylation of the phospholipid phophatidylethanolamine or ethanolamine plasmalogens.[73] Choline can then be formed by hydrolysis of the resulting phospholipids.[74]

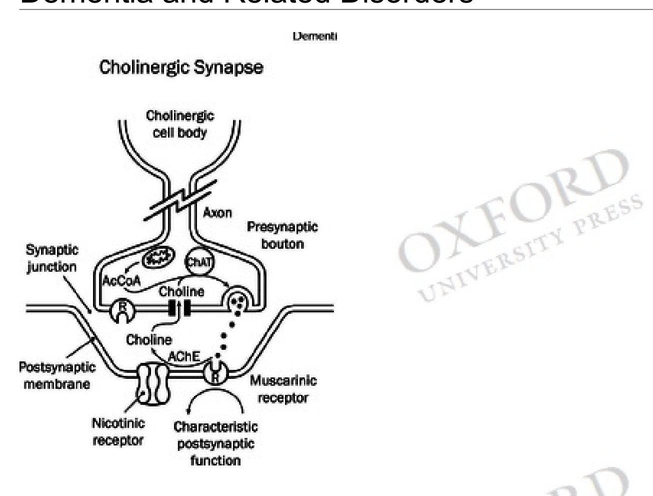




Figure 7–3.
Schematic diagram of a cholinergic synapse in the cerebral cortex. Acetylcholine is formed from choline and acetyl-coenzyme A (AcCoA) and released into the synapse (black dots). In the synapse, acetylcholine binds to muscarinic (R) or nicotinic receptors involved in memory formation. Acetylcholine is rapidly degraded by acetylcholinesterase (AChE) within the synapse, and choline is taken back up into the pre-synaptic nerve terminal. The commonly used cholinesterase inhibitors used to treat AD act by inhibiting the breakdown of acetylcholine.

The other major source of intraneuronal choline is the uptake of choline from the synaptic cleft into cholinergic axons after it is formed by hydrolysis of acetylcholine by acetylcholinesterase (AChE).[70,75] Both high-affinity and lowaffinity uptake systems for choline have been characterized. Dietary choline administered to rats has been reported to raise brain acetylcholine concentrations.[76] The high-affinity system may be saturated at low plasma concentrations; the low-affinity mechanism is the most likely to mediate the increase in tissue choline occurring after plasma choline rises. Experimental evidence also suggests that the extent to which a cholinergic neuron synthesizes more acetylcholine when provided with additional choline is related to its physiologic activity.[77]

Acetylcholine released from cholinergic nerve endings may act at both muscarinic and nicotinic receptors.[78,79] Muscarinic receptors appear to predominate in the brain and are of greatest importance for cognitive function, but nicotinic receptors also play an important role.[80,81] Five G-protein-linked muscarinic receptors have been identified, with M1 receptor stimulation and M2 inhibition being closely linked to cognition. Activation of the M1, M3, and M5 subtypes may have the potential to inhibit formation of β-amyloid and hyperphosphylation of tau protein involved in the pathogenesis of AD.[79] Presynaptic M2 muscarinic receptors appear to provide a feedback inhibition of acetylcholine release, since muscarinic blockers such as scopolamine and atropine enhance acetylcholine release. The electrophysiologic actions of acetylcholine appear to be mediated by both second-messenger systems and ionic channels, but the molecular action of acetylcholine in memory processes is not precisely understood.[82,83] A number of physiologic studies have suggested that it may augment responses induced by other excitatory transmitters.[84,85] Acetylcholine pathways may regulate receptivity to memory storage in localized regions of the cerebral cortex.[83]

Acetylcholinesterase enzyme activity responsible for hydrolysis of acetylcholine released into the synapse is found predominantly associated with presynaptic nerve terminals.[65] Lesions of the basal forebrain in animals lead to a marked depletion in AChE activity in cortex. Inhibition of AChE activity substantially enhances the effect of acetylcholine and this strategy has been exploited to attempt to treat AD as described in detail throughout the rest of this chapter.[86]

Degeneration of Cholinergic Synapses and AD Pathology

Synaptic connections among neurons in the cerebral cortex appear to be the earliest targets of AD, and loss of synapses is far more pronounced than neuronal death early in the disease.[87,88] As the synaptic network of the cortex becomes disrupted, the neuropathologic hallmarks of this condition, including neurofibrillary tangles, granulovacuolar degeneration, and neuritic plaques, appear.[89] Silver-staining neurites surrounding the amyloid core of the plaque represent the wreckage of destroyed neuronal circuitry.[89] There is a close association between the density of neuritic plaques and the severity of dementia.[90]

Loss ofthe cholinergic innervation of the cerebral cortex originating in the basal forebrain is prominent early in the course of AD.[91–93] In postmortem brain from patients with advanced AD, there is a close coordination between the loss of ChAT activity, severity of dementia, and plaque density (Figure **7–4**).[94] Loss of ChAT reflects progressive destruction and disease in cholinergic synaptic terminals. Reduction is greatest (−70% to −90% of control) in areas such as temporal and parietal cortex, which are most severely affected morphologically in AD. Loss of ChAT activity and acetylcholine synthetic capacity and a reduction in the ability of cortex to take up radioactive choline into pinched-off synaptic terminals have been found in cortical biopsy specimens of patients with relatively early AD.[95–97] One study found that the in vitro estimate of acetylcholine synthesis in cortical biopsy specimens was significantly correlated with the rating of cognitive impairment in AD patients.[98] The activity of AChE associated with cholinergic axons is also severely diminished in AD, and AChE staining is seen in degenerating neurites.[99]

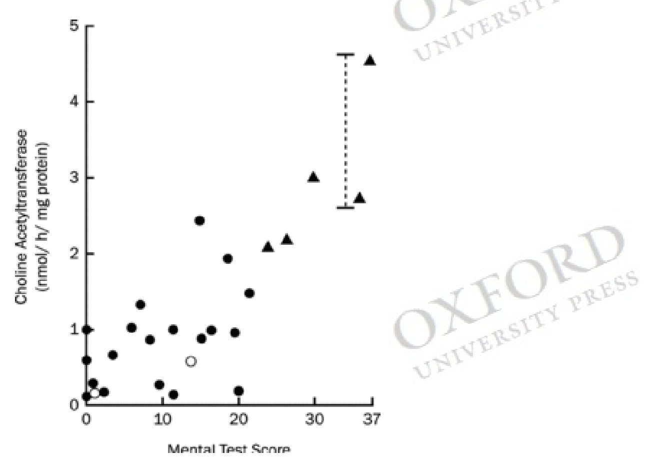




Figure 7–4.
Relationship between postmortem assay of ChAT activity in temporal cerebral cortex and performance in a simple memory and information task within six months prior to death

in a group of elderly patients. Symbols indicate individual patients with depression (triangles), AD (circles), combined Parkinson's and AD (open circle). Dotted line represents mean and standard deviation for age-matched control group. Based on data from Perry.[94]

In contrast to the early changes in synaptic connections in the cortex, cholinergic neurons in the basal forebrain are generally preserved until late in the disease, although they may be smaller than normal.[100] This suggests that the disorder of cholinergic neurons may begin in the cortex and act retrogradely to affect neurons in the basal forebrain.[101] A morphologic study of postmortem brain found that the number of neurons in the nucleus basalis staining for the P75 neurotrophin receptor was reduced in both MCI and AD, although ChAT-positive neurons were preserved.[100,102] Another study of brain tissue from individuals with MCI and mild AD found no reductions in ChaT activity compared to controls in parietal, temporal, or cingulate cortex, and increased activity in hippocampus and superior frontal cortex.[103] Samples from patients with established AD had reductions in ChAT activity compatible with previous studies. Upregulation of ChAT activity in frontal cortex and hippocampus, as well as up-regulation of the choline transporter found in another study,[104] might reflect compensation by cholinergic neurons as synaptic function fails during the transition from MCI to AD. In contrast to the severe decrease in biochemical markers for cholinergic nerve terminals, little change has been found in muscarinic receptors in the postmortem AD brain.[105–107] Multiple subtypes of nicotinic ligand-gated ion channel receptors have also been examined in AD and are found to be variably reduced in different regions of the brain.[108,109]

Possible Role of Cholinergic Deficit in Aβ Accumulation

The severity of the cholinergic deficit and other pathological changes, such as deposition of Aβ and tau pathology, are generally correlated in established AD, but the relationship between them has remained puzzling. Although the cholinergic hypothesis of AD was prominent in the 1980s, it has been overtaken by the hypothesis that deposition of amyloid is the primary trigger for the disorder. However, there has been renewed interest in how the cholinergic deficit might trigger abnormal APP processing. Caccamo and colleagues recently reported that administration of the M1 muscarinic agonist AF267B to the 3xTg-AD transgenic mouse model of AD led to reduced deposition of Aβ and tau pathology as well as improved spatial memory.[110] Administration of the M1 antagonist dicyclomine led to increased deposition of these proteins in the model. One possible mechanism for this effect could be modulation of β-secretase BACE1 activity, which is controlled by muscarinic receptor activity (Figure **7–1**).[111] It has also been proposed that the A7 nicotinic receptor might play a similar role to facilitate normal APP processing in neurons in the hippocampus.[112] This newly recognized relationship between acetylcholine and APP processing could have implications for future therapies.

Amino Acid Neurotransmitter Abnormalities in AD

Abnormalities have been found in both glutamate and GABA systems in the cerebral cortex in brain tissue from patients with AD. Many large pyramidal neurons use glutamate as their neurotransmitter, and they are involved in important excitatory circuits such as the perforant pathway, which carries information from the entorhinal cortex into the dentate gyrus of the hippocampus.[113] Projections from excitatory neurons in the CA1 and subiculum of the hippocampus form the major efferent pathway for information that leaves the hippocampus and will be stored in distributed parts of the cerebral cortex.[114] The entorhinal cortex, perforant pathway, subiculum, and CA1 regions contain large numbers of plaques and neurofibrillary tangles early in AD, disrupting the ability of this region to encode new memories.[113] Sodium-dependent binding of 3H-D-aspartate to presynaptic excitatory amino acid (EAA) uptake sites on nerve terminals is reduced in the temporal cortex.[115] Glutamate-like immunoreactivity has been found in neurons containing neurofibrillary tangles in 50%–70% of CA1/CA2 pyramidal cells of the hippocampus.[116] Postsynaptic receptors for glutamate measured in vitro by autoradiography using 3H-glutamate to measure binding to NMDA-sensitive sites are reported to be reduced in AD cerebral cortex and hippocampus by 50%–85%.[107,117–119] Glutamate receptors of the NMDA type are coupled to an ion channel, which can be labeled using the dissociative anesthetic (phencyclidine) receptor site; these binding sites are also reduced in AD (Figure **7–5**). There may also be alterations in specific slice variants for the NR1 subunit of the NMDA receptor in patients with AD that make neurons more sensitive to injury.[120] These observations suggest the presence of a major disruption in excitatory synaptic function in AD.[121] Excitatory amino acid neurotransmitter systems, especially the channel containing the NMDA/dissociative anesthetic site, have been implicated in learning and memory and the associated electrical phenomenon of longterm potentiation in the hippocampus. Degenerative changes in EAA pathways involved in learning may be important in the pathogenesis of dementia, and excessive excitation mediated by these pathways could play a role in progressive neuron degeneration in AD.[122] Excessive excitation of the NMDA receptor induces calcium overload and metabolic derangements associated with metabolic or oxidative stress, in which oxygen free radicals are generated.[123] Amyloid β oligomers have been shown to interact directly the NR1 subunit of the NMDA receptor to activate oxidative stress in hippocampal neurons in culture, an effect that is blocked by the NMDA blocker memantine.[50] Memantine is an open-channel blocker of the NMDA receptor, and it is has recently been approved by the FDA for treatment of AD as described further on in this chapter.[124]

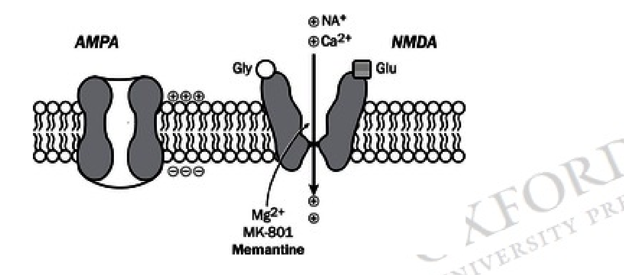


Figure 7–5.
Schematic diagram of excitatory glutamate receptors in the brain and the mechanism of action of memantine, which is approved for the treatment of dementia in AD. Most of the fast excitatory activity of the brain is mediated by AMPA receptors (see Chapters 1 and 3). NMDA type glutamate receptors are involved in learning and memory, but they open only when AMPA receptors are also active, and when the neurotransmitters glutamate and glycine are available to activate them. Magnesium (Mg++), MK-801 and memantine all block the NMDA channel, and Mg++ usually blocks the channel when it is inactive. Drugs like MK-801 are powerful blockers of the NMDA channel, but also produce delirium and other psychotropic effects. On the other hand, memantine is an uncompetitive channel blocker that blocks high activity, but not lower level physiological activity. It may act by reducing excitotoxicity produced by amyloid-β.

Inhibitory GABAergic neurons, which are predominantly small interneurons in the cerebral cortex, are also affected at a relatively early stage in AD.[125] These neurons play an important role to control excitability in the cortex as well as in cortical plasticity.[126] Studies of postmortem brain tissue from patients with AD researchers demonstrated a 70% loss of uptake of tritiated GABA into nerve terminals in the cortex and hippocampus in AD.[127] This is consistent with reports that the synthetic enzyme for GABA, glutamate decarboxylase (GAD), is also reduced in postmortem brain from patients with AD.[128–130] The neuropeptide somatostatin, which is colocalized with GAD in some neurons, has also been found to be decreased in AD brains.[131] These findings suggest that disruption of GABAergic neuron terminals could surpass the loss of cell bodies. GABA and benzodiazepine receptors have also been reported to be reduced in brain tissue from patients with AD.[107,132–134] Loss of inhibitory GABAergic innervation in AD may contribute to enhanced excitability that contributes to progressive neuronal degeneration as well as to behavioral changes such as psychosis.[135,136]

Deficits in Catecholamines in Cortex

Degeneration of the locus coeruleus and a reduction in biochemical markers for the noradrenergic projection from the pons into the cerebral cortex are common findings in AD (Figure **7–2**).[137] Some studies suggest that there is a greater reduction in cortical norepinephrine concentrations in younger patients with AD than in older patients. One group found a 64% reduction in endogenous cortical norepinephrine in cortical biopsy specimens from patients younger than age 80 with AD, and a 50% increase in the norepinephrine metabolite 3-methoxy-4-hydroxypenylglycol (3-MHPG).[98] This metabolite change is not reflected in cerebrospinal fluid (CSF). In contrast, biopsied patients

aged 80 and older had a reduction in endogenous norepinephrine of 38% and no significant change in MHPG. The increased turnover of norepinephrine suggests that there may be compensation for the destructive processes associated with AD in younger patients. Despite the loss of presynaptic noradrenergic markers, the density of postsynaptic receptors for alpha-1, alpha-2, and beta-adrenergic receptor subtypes in the hippocampus and in temporal cortex has generally been reported to be normal.[138] However, specific subunits of the α2-adrenergic receptors have been reported to be reduced in the hippocampus in AD.[139] Noradrenergic deficits in AD have been linked to behavioral disturbances related to attention and working memory.[140] In contrast to the noradrenergic innervation, there does not appear to be a significant reduction in dopamine concentrations in the cerebral cortex of patients with AD.[141,142] Some studies have reported low concentrations of the endogenous dopamine metabolite homovanillic acid (HVA) in CSF of patients with dementia, but these appear to have disorders such as dementia with Lewy bodies rather than AD.[143] Elevated CSF HVA has been observed in patients with AD and delirium.[144]

Serotonin Deficits in AD

There are a number of changes in biochemical markers for serotonin neurons projecting to cerebral cortex that are probably related to the high incidence of depression, agression, and other neuropsychiatric disorders in patients with AD.[145] Deficits have been found in levels of serotonin (5-HT), 5-HT uptake into serotonin nerve terminals, and the serotonin metabolite 5-hydroxyindoleacetic acid in cerebral cortex from AD patients.[146] Recent studies also reported decreased neurons and increased plaques in the dorsal raphe nucleus in the midbrain, which is the origin of serotonin projections to the cortex.[147] There is also a marked reduction in receptors for serotonin measured in postmortem brain and using PET scanning to assess specific subtypes including 5HTA1 and others.[148–151] Serotonin receptor subtypes 5HT2A and 5HT6 are reduced by approximately 40% in prefrontal cortex of patients with AD, and are thought to be important in neuropsychiatric manifestations.[148] Subtypes 5HT4 and 5HT6 appear to play a role in cognition in the brain, and they may be targets for future therapy to enhance cognition in AD.[152] Specific serotonin receptor polymorphisms have also been associated with psychosis in patients with AD.[153] Antagonists of the 5HT1A receptor have also been proposed to enhance cognition.[154] The serotonin system is a potentially important target for development of future drugs for AD, both for managing behavior and depression and enhancing cognition.[155]

Neuropeptides

The peptide neurotransmitters and modulators, including cholecystokinin, neuropeptide Y, and somatostatin, are found in relatively high concentrations in the cerebral cortex, while vasoactive intestinal peptide, substance P, corticotropin releasing factor (CRF), adrenocorticotropic hormone, and dynorphin are found in smaller concentrations.[156–158] These peptides are localized predominantly in GABAergic interneurons, especially in cortical layers 2, 3, and 6 and in the hippocampus.[158–160] Major reductions in somatostatin were reported in most cortical areas in postmortem specimens with AD.[158,161,162] Reinikainen and associates found a 42% decrease in somatostatin immunoreactivity in frontal cortex, a 28% decrease in temporal cortex, and a 42% decrease in parietal cortex in AD.[163] They reported a correlation between decreases in ChAT activity and somatostatin in some brain areas and found reductions in CSF somatostatin that correlated with psychologic test scores. Severely demented patients showed lower somatostatin-like immunoreactivity than moderately demented individuals, but this difference was not statistically significant. Other researchers found low CSF somatostatin levels in patients with AD, correlating with performance on neuropsychologic testing, but there was no relationship to the duration of AD.[164] Cerebrospinal fluid somatostatin levels correlated with the overall cerebral glucose utilization rates, especially in the posterior parietal lobe.[165] Both somatostatin and neuropeptide Y have been identified in the degenerating neurites in senile plaques. Concentrations of CRF-like immunoreactivity are also reduced in Alzheimer's cortex; the change is significantly correlated with decrements in ChAT activity.[156] In contrast to the reductions reported in somatostatin and CRF in AD, levels of the endocrine neuropeptide galanin are elevated in the nucleus basalis and in terminal fields of the cholinergic projections to cortex.[157,166] Galanin is colocalized with acetylcholine in the large cholinergic neurons in the nucleus basalis and has been shown to inhibit acetylcholine release. It produces cognitive deficits in animals, and it has been proposed that up-regulation in AD could contribute to cognitive impairment. On the other hand, galanin has also been shown to attenuate Aβ toxicity.[167] Preclinical studies suggest that drugs that activate somatostatin signaling or block the effects of galanin could have some potential as treatments for AD.[168,169]

Membrane Phospholipids

Wurtman suggested that cholinergic deficits in AD might be linked to a deficit in phosphatidylcholine (PC), which can serve as a source of choline needed for acetylcholine synthesis. Phosphatidylcholine is one of several phospholipids that are abundant in neuronal membranes and serve as major structural elements.[170] It has been estimated that PC represents 8% of membrane-bound choline, making it a potential cellular reservoir of free choline. Electrical stimulation of brain slices causes release of acetylcholine and a decline in levels of membrane PC, which can be replenished by adding choline.[170] This observation suggested that during states of high activity, cholinergic neurons might maintain their rate of choline conversion to acetylcholine at the expense of structural membrane PC, resulting eventually in cholinergic neuron destruction. This work led to the hypothesis that cholinergic neurons might be vulnerable in AD because they are the only cell type that uses PC both as a structural component of the membrane and as a reservoir for acetylcholine synthesis. Studies utilizing 31P-NMR have shown differences in phospholipids in the brains of patients with AD compared to controls, although it is not clear how they are related to the cholinergic deficit.[171,172] Levels of choline measured with brain 1H-NMR spectroscopy have been reported to be higher in patients with AD, which may be related to gliosis or membrane breakdown rather than changes in substrate level.[173] A number of clinical trials of dietary choline or phosphatidylcholine (lecithin) to increase acetylcholine production have been conducted, but there is little clinical evidence to support this approach as described further on in this chapter.[174]

Phospholipids are also involved in signaling cascades for learning and memory activated by muscarinic and glutamate metabotropic receptors. Myoinositol is used to synthesize phosphatidylinositol 4, 5-bisphosphate (PIP2), which is converted to inositol 1,4,5-triphosphate (IP_3) and diacylglycerol in response to receptor stimulation.[175] Proton magnetic resonance spectroscopy (H-MRS) in patients with AD and transgenic mouse models has shown elevations in myoinositol and reductions in the neuronal marker n-acetyl aspartate (NAA) early in the course of the disease.[176–180] However, the significance of these changes for cell signaling is unclear as myoinositol is also considered to be a marker for neurogolia.[178]

Oxidative Stress

Oxidative stress due to energy failure and mitochondrial dysfunction also appears to play an important role in the pathogenesis of AD and occurs early in the course of the disease.[8,181] Early metabolic studies of postmortem Alzheimer brain tissue identified abnormalities in glucose metabolism and reductions in the activity of the glycolytic enzymes, hexosekinase, aldolase, phosphohexoseisomerase, and phosphoglyceromutase.[146,182] Reduced activity of succinate dehydrogenase activity also suggested mitochondrial dysfunction.[183] In contrast to the reduction in glucose metabolism in cerebral cortex reported in PET studies of patients with AD,[13] examination of biopsied cerebral cortex in vitro demonstrated an increase in the oxidation of U-14-C glucose to 14-C02.[184] Studies of cultured skin fibroblasts from patients with AD also showed that glucose metabolism is increased and mitochondrial activity is decreased.[185] This raises the possibility that some patients with AD have generalized disorders of mitochondrial function that predispose them to oxidative stress.[186] Similar abnormalities in mitochondria have been suggested to play a role in AD pathology seen in individuals with Down syndrome.[187,188]

A defect in mitochondrial energy metabolism could contribute to alterations in neurotransmitters as well as other neuropathology seen in AD. Both acetylcholine production and glucose incorporation into amino acids have been shown to be reduced oxidative metabolism in aged animals.[184,189] Depolarization of neuronal membranes associated with mitochondrial impairment also leads to passive opening of NMDA-type glutamate receptors that may contribute to pathology in AD.[123] Oxidative stress associated with mitochondrial impairment can also activate signaling pathways such as β-secretase that enhance amyloidogenic APP processing towards Aβ.[190] Phosphorylation of tau protein is also activated by oxidative stress.[191] Amyloid β induces free radical generation in neurons and binds to mitochondrial proteins including Aβ-binding alcohol dehydrogenase (ABAD), as well as inhibiting the activities of α-ketoglutarate dehydrogenase and cytochrome oxidase.[192] A vicious cycle of oxidative stress and altered APP processing appear to contribute to the degenerative course of AD, as Aβ oligomers have been shown to cause oxidative stress through an NMDA receptor dependent mechanism.[50] Oxidative stress can also result from hypoxia and ischemia in patients with vascular dementia and cerebrovascular disease, and this may provide a rationale for the overlap in the cognitive impairments associated with these diverse disorders.[26]

Therapy for ad

Cholinesterase Inhibitors

Currently there are three cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, that have been approved by the Food and Drug Administration (FDA) and are used widely to treat patients with AD (Table 7–3).[4,193] Tacrine, another drug in this class, was approved for mild to moderate AD in the 1990s but is usually not prescribed because of a high rate of hepatotoxicity. Donepezil is approved for mild to severe AD, while rivastigmine and galantamine are approved for mild to moderate disease. These drugs act by increasing the availability of acetylcholine at cholinergic synapses where it can interact with muscarinic and nicotinic receptors. The rationale for this therapy is based on the neurochemical abnormalities in AD brain tissue and several randomized, double-blind trials showing that physostigmine, a rapidly acting AChE inhibitor, produced a small but measurable improvement in memory in normal subjects and patients with AD.[194–196] A 2006 Cochrane review of the literature on cholinesterase inhibitors found 41 clinical studies of these drugs in patients with AD and summarized efficacy data on 10 that were randomized, double-blind, placebo-controlled trials in patients with mild or moderate dementia.[61] These studies showed small but highly significant improvements on the ADAS-Cog (cognitive scale of the Alzheimer's Disease and Associated Disorders Scale), as well as improvements in global clinical state, activities of daily living, and behavior. There was a trend for improvements in patients with severe dementia as well, but there were data from only two trials.[197,198] Another doubleblind, placebo-controlled trial studied patients treated with severe AD in nursing homes given donepezil over six months and found significant improvement in the Alzheimer's Disease Cooperative Study activities of daily living inventory for severe AD (ADCS-ADL-severe).[199] More patients (29%) left these trials because of nausea, vomiting, or diarrhea in the treatment group than in the placebo group (18%).[61] Very few trials have compared these drugs with each other. A trial in which rivastigmine and donepezil were compared showed no difference in efficacy between them, although there were fewer side effects with donepezil.[200] Studies of cholinesterase inhibitors have generally shown a positive impact on behavioral and neuropsychiatric signs, including hallucinations, apathy, and distractability.[4,201] Reduction in caregiver burden, delay in nursing home placement, and improvement in quality of life have also been reported.[202,203] Treatment with cholinesterase inhibitors has been generally accepted as a part of the symptomatic treatment of AD in the United States, but assessment by a group in the United Kingdom concluded that treatment with donepezil was not cost effective.[6,204–206] Although the cholinesterase inhibitors provide symptomatic improvement, there is no evidence that they change or reverse the degenerative course of the disease.

Table 7–3 Medications Commonly Used to Improve Cognition in AD

Drug	Target	Initial/Maintenance Dose	$t_{1/2}$ (h)	Common Side Effects
Donepezil (Aricept)	inhibits acetylcholinesterase	I: 5 mg, 1x/d, for 4–6 wk; M: 10mg, 1x/d	60–90	nausea, diarrhe, vomiting
Rivastigmine (Exelon)	inhibits acetylcholinesterase and butyrlcholinesterase	I: 1.5 mg, 2x/d for 2 wk; Increase 1.5 mg per dose every 2–4 wk; M: 3–6 mg, 2x/d	2	nausea, diarrhea, weight loss, vomiting
Galantamine (Razadyne)	inhibits acetylcholinesterase activates nicotinic receptors	I: 4 mg, 2x/d for 4 wk; Increase 4 mg per dose every 4 wk; M: 8–12 mg, 2x/d	5–7	nausea, vomiting, diarrhea, dizziness
Memantine (Namenda)	uncompetitive blocker at the NMDA glutamate channel	I: 5 mg/d; Increase 5 mg every 2 wk; M: 10 mg, 2x/d	60–80	hallucinations confusion dizziness headache

Although the three commonly used cholinesterase inhibitors have similar efficacy, there are some significant differences among them with respect to metabolism and duration of action (Table 7–3). Donepezil is slowly absorbed and has a long half-life of 60–90 hours. It is partially metabolized by hepatic cytochrome p450 enzymes, but a large amount is also excreted unchanged in the urine. It can be give once daily and its metabolism can be affected by other drugs that are similarly metabolized, such as cimetidine, ketoconazole, or fluoxetine.[4] In contrast, rivastigmine has a short elimination half-life of two hours, and is not metabolized by the liver.[207] In addition to requiring dosing at least twice a day, coadministration with food to delay absorption may be advisable because its rapid absorption may increase side effects. Galantamine has an intermediate half-life of five to seven hours compared to donepezil and rivastigmine, but is metabolized by the liver like donepezil.[208] All three drugs may have more side effects when therapy is initiated so starting with a low dose and advancing slowly is advisable.

There are also differences between these drugs with respect to mechanism of action, which distinguish them from each other (Table 7–3). Donepezil and galantamine are relatively selective inhibitors of acetylcholinesterase in contrast to butyrlcholinesterase, which makes up about 10% of the total cholinesterase activity in the brain. In contrast, rivastigmine inhibits both AChE and butyrlcholinesterase.[209] It has been proposed that butrylcholinesterase may compensate for lost AChE and become a useful therapeutic target in certain patients. In addition to inhibiting acetylcholinesterase, galantamine also acts at nicotinic acetylcholine receptors to increase presynaptic acetylcholine release and activate postsynaptic neurons.[210–212] These drugs are generally discontinued after three months if no beneficial response is apparent. Differences in mechanisms, absorption, metabolism, and elimination half-life may make it worthwhile to switch from one drug to another in certain patients in whom there is lack of efficacy or intolerable side effects.[213,214] It is often difficult to distinguish AD from vascular and other causes of dementia. Anecdotal reports suggest that the cholinesterase inhibitors may be useful in some patients with vascular dementia, but no large scale controlled trials have been reported.[215] Rivastigmine has been reported to provide some benefit for patients with Lewy body dementia and Parkinson's dementia.[216] Both donepezil and rivastigmine have also been reported to improve cognition in small groups of younger patients with cognitive disorders following traumatic brain injury.[217,219] Cholinesterase inhibitors have also been used in small trials in patients with Down syndrome, autism, and other developmental disorders.[220–224]

Cholinergic Precursor and Receptor Agonist Therapy

In addition to blocking the breakdown of acetylcholine, the function of cholinergic synapses can be enhanced by increasing the concentration choline, a substrate for acetylcholine synthesis, or by directly stimulating postsynaptic cholinergic receptors. Early clinical studies of oral administration of the choline precursor deanol showed no effect on cognition in AD.[225] Oral administration of lecithin (PC) has also been used to provide choline for the synthesis of acetylcholine, but a meta-analysis of 12 randomized trials involving patients with AD, Parkinsonian dementia, and MCI also showed no benefit.[174] Citicoline (CDP-choline), an essential intermediate in the synthetic pathway for PC and other phospholipids, has been shown to be protective in animal models and appears to be safe when administered to humans.[226]

Although no drugs that act primarily as acetylcholine agonists are currently approved by the FDA for treatment of AD, this remains an active area of investigation. Administration of the muscarinic agonist arecoline to patients with dementia has been shown to improve cogntion.[227] Bethanechol, an analogue of acetylcholine that is resistant to cholinesterase activity and lacks significant action at nicotinic receptors, has also been reported to augment memory. Trials with intraventricular infusion of bethanechol were conducted because of its limited blood brain permeability, but benefits were modest at doses that could be tolerated without significant side effects.[96,228,229] The first generation of cholinergic agonists did not perform well in clinical trials because of excessive cholinergic side effects, low bioavailability, and poor selectivity for specific receptor subtypes.[79] Several new compounds with more selectivity in are under clinical investigation. Currently there is considerable interest in the ability of muscarinic and nicotinic agonists to normalize APP processing and tau pathology in transgenic models of AD, as described previously.[110] This suggests that these compounds could have both symptomatic and disease-modifying effects on dementia.

The NMDA Antagonist Memantine

The NMDA glutamate receptor antagonist memantine was approved for use in moderate to severe AD by the FDA in 2004, after being used in Europe for two decades (Table 7–3).[4,230] The rationale for its use is supported by neuropathological and preclinical evidence that glutamate-mediated neurotoxicity, oxidative stress, and excessive calcium fluxing into neurons play a role in the pathogenesis of AD, as described previously.[231] Meman tine has the potential to block this toxicity by preventing glutamate from causing high amounts of calcium to travel through the NMDA channel. It is called an uncompetitive blocker of the NMDA receptor because it binds to a site within the open NMDA channel where it antagonizes the effect of pathologically high amounts of glutamate, but not lower physiological amounts (Figure **7–5**).[124] Too much blockade of the NMDA glutamate receptors and/or channels by compounds such as phencyclidine or dizocilpine (MK-801) has been shown to cause severe memory disturbances, hallucinations, or coma. Physiological modeling of memantine's effect on the NMDA channel indicates that its positive charge leads it to bind inside the open channel where it can block calcium from flowing into neurons. However, memantine can also leave the channel quickly as it closes when the glutamate level drops. Through this mechanism, the drug blocks high amounts of glutamate mediated activation of NMDA receptors but leaves normal physiological activity intact.[124] The drug has similar but milder effects on 5HT3 serotonin receptors and nicotinic receptors.[124] From a mechanistic standpoint, memantine has an entirely different action from the cholinesterase inhibitors.

Memantine is absorbed completely and has a half-life of 60–80 hours with predominantly renal elimination without hepatic metabolism (Table 7–3). Clinical trails of memantine indicate that it is well tolerated without major side effects and leads to modest symptomatic improvements, although hallucinations, confusion, dizziness, and headache can occur.[232,233] Some case reports suggest that patients with Lewy body dementia are more prone to develop hallucinations and delirium while taking memantine.[232,234] A 28-week trial in patients with moderate to severe AD showed that patients receiving memantine had a better outcome than those receiving placebo on the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC Plus) global score, the ADCS-ADL, and the Severe Impairment Battery.[235] Several other studies reported benefit including a study that included patients with vascular dementia. A study of 404 patients with AD tested the effect of memantine used with the cholinesterase inhibitor donepezil and found that the memantine-donepezil combination led to greater benefit than the donepezil-placebo combination.[236] Larger studies are needed to detect clinically important benefits, especially in patients in the early stages of dementia. Although memantine produces modest improvement in cognition and behavior, there is no evidence that it actually modifies the course of AD.

Therapy for Behavioral Disorders

Depression, psychosis, aggressive behaviors, and other psychiatric disorders occur in up to 80% of individuals with AD and are often the most prominent and troublesome aspects for caregivers.[237,238] Cholinesterase inhibitors have been shown to provide some benefit for behavior, but antipsychotic drugs, anxiolytics, and sedatives are commonly prescribed as well. Haloperidol, risperidone, and olanzapine have all been shown to be effective for psychotic features such as delusions and hallucinations in AD, and there is some evidence that risperidone is more effective for suppressing aggressiveness.[239] However, a meta-analysis of 17 placebo-controlled trials of atypical neuroleptics in people with dementia suggested an increase in stroke and mortality compared to first-generation neuroleptics.[240,241] In addition, a recent double-blind, placebocontrolled trial of more than 400 outpatients with AD and psychosis, aggression, and agitation treated with the atypical antipsychotic drugs olanzapine, quetiapine, risperdone, or placebo found no differences among treatment groups when adverse events were taken into account.[242] Although the atypical antipsychotic drugs were more effective than control, discontinuance due to side effects including sedation, extrapyramidal signs, and weight gain offset these advantages. This suggests that these drugs need to be used judiciously at low doses.

Depression in patients with dementia is generally treated with selective serotonin reuptake inhibitors (SSRI) started at low doses and escalating carefully.[4,238] Selective serotonin re-uptake inhibitors are generally preferred to tricyclic antidepressants because the latter drugs have anticholinergic effects that can worsen memory, antagonize the effects of cholinesterase inhibitors, and potentially cause delirium. Numerous trials have been carried out on the efficacy of SSRIs and the outcomes have been mixed.[145,243,244] Sleep disturbances, especially loss of normal circadian sleep-wake patterns, are also common in AD and often disturbing to caregivers.[245] Alzheimer's disease pathology has been reported in the suprachiasmatic nucleus of the hypothalamus, which regulates circadian rhythms, and decreased melatonin secretion has been documented in several studies.[246,247] Exogenous melatonin has been reported to improve sleep in some patients with AD, and ramelteon, a new melatonin receptor analogue, is undergoing clinical trials.[247] Caregiver education in sleep hygiene and behavior-management training for patients combined with daily walking and exposure to a light box have also been reported to produce significant improvement in patients with AD in a controlled trial.[248] These methods are likely to be more effective than long-term use of sedatives or benzodiazepines, which can degrade performance over time.

β-Amyloid Directed Therapies

There are no approved medications that modify the course of AD by reducing the burden of amyloid and soluble Aβ protein in the brain, but preclinical studies show promise for this approach in the future.[5,54] Strategies have focused on inhibiting γ-secretase and BACE that cut Aβ42 from the larger APP protein (Figure **7–1**).[249] The success of compounds that inhibit γ-secretase is potentially limited by the fact that there are other substrates for this enzyme that are involved in critical cellular pathways, including cellular immunity.[250] However, (R)-flurbiprofen is an investigational drug that inhibits γ-secretase but appears to reduce Aβ42 selectively with less effect on other substrates for the enzyme.[251] A phase II trial of this compound in patients with AD showed statistically significant improvement in cognitive and behavioral performance and BACE inhibitors are also under active investigation.[252] Passive immunization with antibodies against Aβ42 has also been shown to increase the clearance of Aβ and improve cognitive performance in several mouse models of AD.[253] This approach has also been used in a clinical trial of active immunization against Aβ42 in humans, but the trial was stopped due to development of meningoencephalitis in some subjects.[254] Positive trends suggesting that this approach reduced amyloid burden and stabilized cognitive function in some patients in the trial may lead to continuation of this research with a modified protocol.[255,256]

Another approach to modifying Aβ is to reduce its aggregation and deposition into amyloid plaques, and several antiaggregants are under study.[54] Transiposate is a drug that resembles glycosaminoglycan (CAG) that reduces plaques and CSF concentrations of Aβ in transgenic mouse models of AD.[249] Transiposate and an antiaggregant polypeptide called O-CLN have both shown activity to improve cognition in patients with mild AD in early clinical trials. Agonists for peroxisome-activated receptor-γ, including rosiglitazone and pioglitazone, can reduce Aβ levels and plaque deposition in animal models and have also shown some activity in patients with AD.[257] Rosiglitazone has been shown to stimulate mitochondrial biogenesis and improve glucose metabolism in mouse models, suggesting a possible mechanism for their antiamyloid effects.[258]

Antioxidants and Vitamins

As described previously, there is considerable evidence that oxidative stress plays an important role in the pathogenesis of AD. Vitamin E (α-tocopherol) has strong activity as an antioxidant and has been used along with selegiline, a selective inhibitor of monoamine oxidase B(MAO-B) in a double-blind, randomized controlled trial in patients with moderate AD.[259] Although there was no improvement in cognition, vitamin E treatment was associated with a delay in need for institutionalization. In the Cache County study, use of vitamine E and C supplements together, but not alone, was associated with lower incidence of AD.[260] However, data showing that high doses of vitamin E (>400IU/day) might be associated with excess mortality, as well as failure of additional trials of vitamin E to prevent AD or prevent conversion from MCI to AD have diminished enthusiasm for this approach.[261] Other antioxidant compounds, including oral preparations of the mitochondrial coenzyme Q10 and the plant extract ginkgo biloba (EGb 761), are widely used by elderly individuals and have been recommended for treatment of dementia.[181] Both are widely available in health food stores. A placebo-controlled trial of ginkgo in patients with AD showed small improvements in the ADAS-cog after one year.[262] Meta-analysis of data available in 2004 on ginkgo, donezepil, rivastigmine, and galantamine showed small improvements for all four therapies, although the data for cholinesterase inhibitors were more consistent than for ginkgo.[263] Patients tolerated all therapies similarly, and ginkgo appears to be safe. A recent randomized placebo-controlled double-blind study that compared donepezil and ginkgo extract in patients with mild to moderate AD over 24 weeks showed similar improvements in the Clinical Global Impression and MMSE scores for both drugs.[264]

Other compounds with antioxidant activity include docosahexaenoicacid (DHA), acetyl-L-carnitine, folic acid, and melatonin. DHA is an abundant omega-3 polyunsaturated fatty acid found in some fish, and a study of subjects in the Framingham Study found that high plasma levels of phosphytidylcholine-DHA were 47% less likely to develop dementia compared to subjects in the lower quartiles.[265] Docosa-hexaenoicacid has also been found to reduce dendritic pathology and memory loss in mouse models of AD.[266]

Acetyl-L-carnitine has been reported to enhance mitochondrial function but has not been shown to improve cognitive function in multiple studies of patients with AD.[267] The rationale for folate therapy relates to evidence that elevated homocysteine has been shown to be a risk factor for both cardiovascular disease and AD.[268] Low folate and high homocysteine have been reported to be independent risk factors for AD.[269] Lipoic acid is a precursor to dihydrolipoic acid, a cofactor for mitochondrial enzymes, and has been suggested as a therapy for AD, but clinical trials have not been reported.[270] Other antioxidants including β-carotene and selenium have not shown activity against AD. Melatonin has been suggested to have antioxidant activity but there are no large scale controlled trials.[271]

Ergoloid Mesylates

Ergoloid mesylates (hydergine) is approved by the FDA in the United States as well as several other countries for treatment of dementia. A mixture of hydrogenated ergot alkaloids including dihydroergocryptine mesylate, it has been reported to have effects on alpha-adrenergic, serotonin, and dopamine receptors as well as an effect on cerebral metabolism.[272] Numerous trials have reported positive effects on patients with dementia, although some have been negative. A systematic review of 19 clinical trials of hydergine for dementia published by the Cochrane group in 2001 concluded that there was a significant effect favoring the drug for the nine trials that used comprehensive rating scales.[273] However, they noted that these conclusions were limited by the fact that all of the randomized double-blind trials were conducted before the advent of consensus-based diagnostic standards for dementia in 1984.

Anti-Inflammatory Drugs

The neuropathology of AD is associated with signs of chronic inflammation, and several large observational studies showed that chronic ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with decreased risk of developing AD.[58] This effect was strongest for individuals who took NSAIDs for longer than two years. Preclinical data showed that ibuprofen, sulindac, and indomethacin decreased Aβ42 levels in cultured neurons.[274] The most prominent target for NSAIDs is cyclooxygenase (COX), which occurs in two isoforms, COX-1 and COX-2.[275] Evidence that COX-2 is responsible formation of prostaglandins associated with inflammation led to the hypothesis that specific inhibitors of this enzyme would be effective for AD. Clinical trails have been initiated with both types of NSAIDs, but there have been no positive results either for prevention of onset or improvement in cognition in patients with AD. New evidence also indicates that COX-2 in the brain is produced in neurons constitutively and it activity is not strongly induced by inflammation. Furthermore, the ability of some NSAIDs to reduce Aβ levels in vitro may not be related to ability of these drugs to inhibit COX. This class of drugs also carries risk of increased cardiovascular and kidney toxicity with long-term use. Taken together, this information indicates that the NSAIDs do not appear to be a promising direction for therapy for AD at this time.

Hormonal Therapy

Hormone replacement therapy (HRT) with estrogen given to women entering menopause has been strongly associated with a lower risk of AD in observational studies, however, prospective clinical trials of female hormones for older women at risk for AD indicate that estrogen may actually increase risk.[276] Hormone replacement therapy with estrogens, with or without progestin, given to women older than age 65 in the Women's Health Initiative Memory Study was associated with a two-fold increase in the risk of AD.[277] These results suggest treating older women with HRT is not a useful strategy for preventing AD, although the effect in younger women remains to be clarified.[276] Basic science data suggests that young healthy neurons may be protected by estrogen but injury may be accelerated in neurons already affected by the disease.[278,279]

Statins

Based on the shared risk factors for AD and cardiovascular disease and preclinical evidence that statins may reduce Aβ deposition in animal models, several epidemiological studies and prospective trials have examined the protective effect of statins.[280,281] Some cross-sectional and case-control studies have suggested that statins lower the risk of AD, but a longitudinal epidemiological study found no relationship between use of statins and onset of AD.[25] Two large randomized, controlled prospective cardiovascular trials did not find any reduction in AD or improvement in cognition associated with use of simvastatin or pravastatin.[282,283] However, cognition was not a primary outcome of these studies. A small double-blind, placebocontrolled, randomized trial of atorvastatin did find significant benefits on cognition, mood, and global function in association with reduction in plasma lipids.[284]

Trophic Factors

Trophic factors such as nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) are of potential importance for AD therapy, although no approved drugs based on this approach are available at this time.[285] Trophic factors would offer support to neurons that are impaired by the underlying pathology in AD. Nerve growth factor is strongly associated with trophic support of cholinergic neurons, while BDNF is synthesized in neurons in response to excitatory synaptic activity.[286,287] Cholinergic neurons retrogradely transport labeled NGF injected into the cortex, and there is a close relationship during development between expression of messenger RNA for NGF and the expression of the acetylcholine synthetic enzyme ChAT. Nerve growth factor acts as a survival factor for injured neurons, and several investigators have hypothesized that administration of NGF or smaller analogues might slow the degenerative process.[288] Nerve growth factor is too large to cross the BBB, but infusion of NGF into the brain in aged rats can improve learning and memory and reverse shrinkage of nucleus basalis cholinergic neurons.[288] Diminished responsiveness of cholinergic neurons in aging may result from defects in intracellular signaling stimulated by the NGF receptor.[289] In a pilot study in the 1990s, patients with AD were given intraventricular infusions of mouse NGF and showed some cognitive improvements, but pain and weight loss led to discontinuation of the trial.[290] Further studies in rodents showed that NGF infusions caused hyperplasia of Schwann cells in the brain. Intranasal administration of NGF and delivery using fibroblasts engineered to express NGF have also been explored.[288] An ongoing phase I clinical trial in early AD in eight patients is using fibroblasts from each patient that have been engineered to express human NGF and then implanted into their own brains in the area of the nucleus basalis.[291] After a mean follow-up of 22 months in six subjects this therapy has been associated with slowing of cognitive decline in some subjects and increased glucose utilization measured by serial PET scans without pain or other untoward side effects. A postmortem study of one patient in the study showed that the NGF stimulated sprouting of the cholinergic nerve fibers.[291] No similar experiments have been done with BDNF, which has been found to be decreased in brains from patients with AD. This approach to delivery of NGF and other growth factors may hold promise for future therapies.

Conclusion

Therapy for dementia and related disorders is a growing field stimulated by the enlarging aged population and a more sophisticated understanding of the neurobiology of cognitive brain disorders. Four drugs, including three cholinesterase inhibitors and memantine, a NMDA glutamate channel blocker, are commonly used to improve cognitive and behavioral manifestations of AD. The cholinesterase inhibitor donepezil is approved for mild to moderate AD while galantamine and rivastigmine are approved by the FDA for mild to moderate dementia. Memantine is the only drug approved for moderate to severe dementia. These drugs produce small but definite improvements in performance but do not appear to make a major impact on the course of the disease. Some differences among the three commonly used cholinesterase inhibitors and memantine may make it worthwhile to change drugs if they do not appear to work in individual patients. Combining a cholinesterase inhibitor with memantine may also make sense in certain patients because their mechanisms of actions are different. Older drugs such as ergoloid mesylates and gingko biloba continue to be used and appear to be active when compared with the cholinesterase inhibitors. In contrast, the NSAIDs and vitamin E appear to have limited usefulness for preventing or modifying the course of AD. Managing the neuropsychiatric and behavioral aspects of AD leads to the prescription of many drugs, but these must be used judiciously because their side effects limit their usefulness. On the horizon may be better ways to modify the course of dementia using approaches that limit amyloidogenic processing of APP and aberrant tau processing into neurofibrillary tangles. Approaches that provide growth factor support for the injured brain may also have some potential.

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Multiple Sclerosis and Related Disorders

Chapter: Multiple Sclerosis and Related Disorders
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Treatment of multiple sclerosis (MS) has changed considerably with the advent of disease modifying therapies (DMTs) including the β-interferons, glatiramer (which is a mixture of synthetic polypeptides), and the monoclonal antibody natalizumabA[2] Magnetic resonance imaging (MRI) has also led to earlier and more accurate diagnosis and staging of MS, and this information has become part of current diagnostic criteria.[3–5] Evidence that MS permanently damages axons as well as white matter and that the disease has often been present for months or years prior to the first episode makes accurate diagnosis and early continuous therapy important for preventing disability.[6–8] Long-term studies suggest that continued therapy is important to prevent relapses and progression of disease, but side effects and discomfort from repeated injections may limit compliance.[2]

Diagnosis and classification of ms

Multiple sclerosis is a relatively common immune mediated inflammatory demyelinating disease of the central nervous system that is more prevalent in females than in males.[9] It is relapsing and remitting in more than 80% of patients (RRMS), and about half of these patients will evolve to a secondary progressive form with or without relapses (SPMS; Table 8–1).[2,10,11] Approximately 10% of patients present with the primary progressive (PPMS) form of the disease. Progressive relapsing MS (PRMS), characterized by progression and acute relapses with or without full recovery, is the rarest form of the disease. The older concept that the diagnosis of MS requires evidence of lesions dispersed in time and space based on history and neurological examination has been replaced by the modified McDonald criteria, which also take into account data from magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), and evoked potential studies (Table 8–2).[10,12] The McDonald criteria allow a diagnosis of MS after a single clinical attack and objective clinical evidence of only one lesion if there is also evidence of dissemination in time or space based on MRI or CSF findings.[10] This is termed a clinically isolated syndrome (CIS).[12] Insidious progression suggestive of MS can also be diagnosed as PPMS after one year, according to the criteria, if there is progression combined with MRI, CSF, or visual evoked potential evidence.[10]

Table 8–1 Major Subtypes of Multiple Sclerosis

Relapsing-remitting (RRMS)	Most common (85%) showing attacks with full or incomplete recovery
Secondary progressive (SPMS)	Half of relapsing-remitting patients become secondary progressive with or without relapses, minor remissions
Primary progressive (PPMS)	Small minority (10%) progressive from the start, with some plateaus or temporary improvements
Progressive relapsing (PRMS)	Least common form with progression from the onset as well as acute relapses and progression between relapses

Table 8–2 McDonald Criteria for the Diagnosis of MS as Modified

Clinical Presentation	Additional Data Needed
2 or more attacks and objective clinical evidence of 2 or more lesions	None
2 or more attacks and objective clinical evidence of 1 lesion	Dissemination in space: Positive MRI or 2 or more MRI lesions + positive CSF or further attack at different site
1 attack and objective clinical evidence of 2 or more lesions	Dissemination in time: MRI or a second clinical attack
1 attack; objective clinical evidence of 1 lesion: clinically isolated syndrome (CIS)	Dissemination in space: MRI or 2 or more MRI lesions + positive CSF and dissemination in time: Positive MRI or second clinical attack
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression and 2 out of 3 of: Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive visual evoked potential; Positive spinal cord MRI (2 or more focal lesions); Positive CSF

Source: McDonald et al, *Ann Neurol*. 2001;50:121–127; Polman et al, *Ann Neurol*. 2005;58:840–846.

Given the value of early treatment with disease modifying therapies, it is useful to determine if a patient with a clinically isolated syndrome is likely to go on to develop full blown MS, and several factors appear to be predictive.[12] For example, a young adult female presenting with painful unilateral optic neuritis and a normal disc exam has a considerably higher risk of developing MS than patients with bilateral painless optic neuritis and disc edema.[12] An abnormal MRI with more than one lesion at baseline in a patient with optic neuritis also raises the risk of developing MS within 10 years to more than 50%, while a normal MRI is associated with a risk of 10%–20%.[12,13] For patients with transverse myelitis, asymmetric lesions with nonedematous small cord lesions carry the highest risk of later MS.[12] Patients with both optic neuritis and transverse myelitis and a spinal cord lesion on MRI extending over three or more vertebral segments probably have neuromyelitis opitca (NMO), with a specific serum antibody against the water channel aquaporin-4.[14] Patients presenting with a CIS and more than 10 lesions on the baseline MRI are more likely to progress quickly to disability level 6 (when patients require a cane or crutch) on the Expanded Disability Status Scale (EDSS).[15,16]

In children, acute disseminated encephalomyelitis (ADEM) may resemble the first episode of MS.[17] Acute disseminated encephalomyelitis is usually a monophasic immunemediated demyelinating disorder that follows infections such as rubeola, rubella, or immunizations. More than 70% of patients with ADEM make a good recovery. Children with MS tend to be older than age 10 while those with ADEM tend to be younger.[18,19] Presenting features such as fever, encephalopathy, lethargy, vomiting, and seizures suggest ADEM, while focal neurological signs without encephalopathy favors MS. Patients with ADEM usually show a lymphocytic pleocytosis in the cerebrospinal fluid. Bilateral optic neuritis is also more common in ADEM while unilateral optic neuritis favors MS.[20] Lesions on MRI localized to the corpus callosum and periventricular white matter are more common in MS, wheras disseminated lesions in the basal ganglia, thalamus, and the cortical gray-white junction favor ADEM.[21] A few patients with ADEM my relapse, so-called multiphasic ADEM, without evidence of new lesions.[22] Consensus definitions for inflammatory demyelinating disorders presenting in children have been proposed.[23,24]

Pathogenesis of ms

Multiple sclerosis is an autoimmune disorder in which activated T-cells, monocytes, and B-cells travel from the bloodstream into the nervous system through the capillary endothelial cells that form the blood brain barrier (BBB; Figure **8–1**).[8,25–27] These cells direct an attack on oligodendroglia and axons causing demyelination and gliosis. Helper T-cells (CD4) and cytotoxic T-cells (CD8) are the major types of T-cells in MS lesions. Autoreactive Th1 CD4 helper T-cells secrete Th-1 proinflammatory cytokines (IL-2 and IFN-γ) and play a prominent role in the attack on myelin in the brain. Leukocytes are initially activated in peripheral lymph nodes and other organs by self-antigens presented by antigen presenting cells (microglia, macrophages, B-cells, and dendritic cells) in association with major histocompatability class II (MHC II) molecules.[25] The identity of these antigens is not known. Several infectious agents including Epstein-Barr virus[28] have been proposed to stimulate this process either by molecular mimicry involving cross-reactivity between self-antigens and infectious agents, or through bystander activation of inflammation triggered by infections. Work on the model of experimental autoimmune encephalomyelitis (EAE) as well as analysis of T-cells in patients with MS suggests that the myelin associated proteins myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG) are important triggers.[26,29]

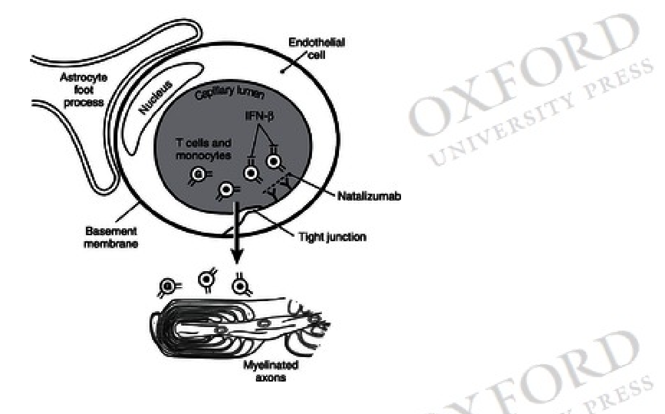


Figure 8–1.
Mechanisms of MS therapies at the level of the blood brain barrier (BBB) and within the brain. Corticosteroids shorten attacks of MS by reducing edema, restoring the integrity of the BBB and diminishing inflammation, but they do not modify its long-term course. In contrast, interferons (IFN-β) modify MS by reducing levels of inflammatory cytokines and increasing antiinflammatory cytokines produced by white cells. The monoclonal antibody natalizumab blocks entry of white cells into the brain by blocking integrin receptors on the capillary endothelial cells that form the BBB. Glatiramer (G) is taken up into helper T-cells, which then cross the BBB and produce anti-inflammatory cytokines in the brain. This amino acid mixture also competes with myelin basic protein for binding sites in antigen presenting cells.

To cross the BBB, activated T-cells and monocytes must traverse the tight junctions of the capillaries in the BBB through an interaction between cell adhesion molecules called integrins on the white cells and complementary ligands on the surface of the endothelial cells (Figure **8–1**).[26,30] This process is enhanced by chemokines secreted by activated endothelial cells. Within the central nervous system (CNS), antigen-presenting cells (e.g., microglia/macrophages) reactivate leukocytes by re-presenting them with self-antigens. The leukocytes then produce proinflammatory cytokines and metalloproteinases, which contribute to the destruction of myelin and axons. Matrix metalloproteinases produced by leukocytes also cleave the basement membrane surrounding capillaries, further weakening the BBB.[31] Proinflammatory cytokines such as interleukin-1, interferon-γ, and tumor necrosis factor alpha (TNF-α) activate microglia, which in turn release nitric oxide, and oxygen free radicals that can damage oligodendroglia and axons.[8] Activated B-cells differentiate into plasma cells and secrete antibodies that bind to target antigens and complement, which further contributes to myelin breakdown. Th2 cells, monocytes, B-cells, activated microglia, macrophages, antibodies, and complement, together with partially digested fragments of myelin axons, form the perivascular plaques that are characteristic of MS.[8,26]

Genetic and environmental factors also contribute to the pathogenesis of MS. Concordance in monozygotic twins is about 35% and the incidence is also elevated in children of affected individuals.[23,32] Polymorphisms in multiple genes may contribute to a risk for the disorder, including alleles for MHC II and TNF-α genes.[33] A genomewide study of risk alleles for multiple sclerosis revealed single nucleotide polymorphisms (SNPs) within the interleukin-2 receptor alpha gene (IL2RA), the interkeukin-7 receptor alpha gene (IL7RA) and multiple SNPs in the HLA-DRA locus that were strongly associated with multiple sclerosis.[34] The incidence is increased in northern Europeans, but migration studies have also suggested that environment is also important when people move at an early age.[35] Some studies suggest that variations in exposure to sunlight, levels of vitamin D, and changes in diet can contribute to the incidence of MS.[36] Diminished exposure to infections in childhood with resulting changes in the immune system have also been proposed to explain a rising incidence of MS in developed societies.[35]

Drug therapies

Corticosteroids

Corticosteroids are useful for treatment of acute relapses of MS to shorten their duration and accelerate recovery, but they have not been shown to improve overall outcome or prevent further relapses.[37,38] Their primary effect is to reduce edema, restore the integrity of the BBB, and diminish inflammation. In the Optic Neuritis Treatment Trial, patients were randomly assigned to receive 1000 mg of methylprednisolone per day by intravenous (IV) infusion for 3 days followed by 1 mg/kg of oral prednisone for 11 days, or 1 mg/kg of oral prednisone for 14 days, or oral placebo.[39] Intravenous methylprednisolone hastened visual recovery compared to prednisone, but there was no difference in visual acuity at six months. Oral prednisone increased the risk of new episodes of optic neuritis. Intravenous methylprednisolone also delayed the onset of MS in these patients but did not reduce the incidence at three years. This trial as well as subsequent studies have led to the recommendation to treat acute relapses with short-term high dose IV methylprednisolone at a dose of 1000 mg/day for 3–5 days.[38–40] The same dose is generally used for patients with isolated optic neuritis or transverse myelitis without a definite diagnosis of MS or for older patients with ADEM.[41–43] For children with acute demyelination who weight less than 30 kg, the usual dose is 30 mg/kg/day.

Disease Modifying Therapies

Interferons

Interferons (IFNs) were the first class of medications to be developed as DMTs for MS.[31,44,45] Interferons are glycoprotein cytokines produced by cells in the immune system in response to foreign antigens associated with viruses, bacteria, and tumor cells. Type I IFNs (α and β) have antiviral properties and IFN-β (fibroblast IFN) has anti-inflammatory effects. Interferon-β reduces the level of inflammatory cytokines while increasing the level of anti-inflammatory cytokines produced by white cells. The molecules also reduce levels of matrix metalloproteinases and improve the integrity of the BBB (Figure **8–1**).[26,31] Interferon-β stimulates Th2 T-cells, which counter the inflammatory effects of Th1 cells and inhibit the migration and proliferation of T-cells. Interferon-β also reduces antigen presentation and improves the function of suppressor T-cells.[26]

Two types of IFN-β are approved for treatment of MS: IFN-β1a and IFN-β1b. Interferonβ1a is produced in mammalian cells wheras IFN-β1b is derived from *E. coli* bacteria. Interferon-β1b was the first DMT to be approved in the United States and it is available in a form to be administered subcutaneously (sc) in a dose of 250 μg every other day (Betaseron; Table 8–3). Interferon-β1a is available in two forms: Rebif (44 or 22 μg sc three times per week) and Avonex (30 μg intramuscularly [IM] once per week). The IFN-β Multiple Sclerosis Study studied patients with an EDSS score of 0–5.5 with at least two exacerbations in the previous two years and found that relapse rates and new MRI lesions were significantly lower in the group treated with IFN-β1b over the next two years.[2] Similar studies have demonstrated the efficacy of sc and IM IFN-β1a for RRMS and SPMS.[46] Additional studies showed that treatment with IFN-βs in patients with a first event suggestive of MS delays conversion to clinically definite MS.[1,2,46–48] Results of the Betaferon/Betaseron in newly emerging multiple sclerosis for initial treatment (BENEFIT) study indicate that early initiation of IFN-β1b in patients with the first event suggestive of MS and at least two clinically silent lesions on MRI prevents development of confirmed disability measured using the EDSS.[49]

Table 8–3 Medications Used to Treat MS

Medication	Preparation	Use	Mechanism of Action
Methylprednisolone	IV 1 gm/d, 3–5 d; less than 30 kg: 30mg/kg	Acute relapses	Reduces edema, inflammation; Repairs BBB
Interferon-β1a	Rebif S.C., 3x/wk Avonex IM 1x/wk	1st line cytokines DMT	↓ inflammatory ↓ MMP ↑ BBB
Interferon-β1b	Betaseron sc Every other day	1st line DMT	As above
Glatiramer acetate	Copaxone sc (synthetic polypeptide mixture)	2nd line DMT	Taken up in Th2 helper T-cells ↓ inflammation Competes with myelin proteins for antigen presentation
Natalizumab	Tysabri IV (humanized monoclonal AB)	Selected nonresponders; use restricted	Blocks integrins required for leukocytes to cross BBB
Mitoxantrone	Novantrone IV	Nonresponders; lifetime limit on total dose due to cardiac toxicity	Inhibits B-and T-cells and macrophages; Antineoplastic

MMT: matrix metalloproteinases; BBB: blood brain barrier

The effects of all three formulations of IFN-β are similar, and the most common side effects are flu-like symptoms, headache, and hypersensitivity.[46,50] They can also stimulate the production neutralizing antibodies (NAb), which may limit their effect.[51] The IM formulation of IFN-β1a is the most convenient and is reported to have the lowest rate of NAbs.[48] Although one study showed that this formulation was not as effective as higher dose sc regimens of IFN-β1a or IFN-β1b in a head-to-head comparison,[48,52] another

comparison found no difference in response rate among them.[53] There is far less data on the use of IFN-β in children with MS, but there do not at this point appear to be major differences in response compared to adults.[19,24]

Glatiramer acetate

Glatiramer (GA; Copaxone) is a mixture of synthetic polypeptides containing the amino acids L-alanine, L-glutamic acid, L-lysine, and L-tyrosine in an average length of 45–100 amino acids. It is given by a daily injection sc.[54] This mixture was discovered to have the capacity to decrease the severity of EAE, the experimental model for MS, and several clinical trials in patients with RRMS demonstrated that GA reduced relapses without major side effects. Several mechanisms have been suggested for its beneficial effect in MS based on its effects in the EAE model (Figure **8–1**). Glatiramer competes with myelin basic protein in antigen presenting cells for binding to MHC II molecules, and this could prevent myelin basic protein from binding to T-cell receptors and activation of the inflammatory cascade.[54] Another important mechanism is that GA is taken up into Th2 helper T-cells, which then cross the BBB, and produce anti-inflammatory cytokines in the brain. These GA-reactive Th2-specific cells may also suppress bystander inflammatory changes and induce neuroprotective factors in the CNS. Glatiramer generally has a good safety profile with few side effects except for some local reactions to injection.[50] A recent randomized double-blind dose comparison study of glatiramer acetate in RRMS at the recommended dose of 20 mg per day sc versus 40 mg per day sc showed that the 40 mg dose was well-tolerated and more effective than the 20 mg dose in new MRI lesions and clinical relapses.[55]

Natalizumab

Natalizumab (Tysabri) is a recombinant humanized monoclonal antibody directed against leukocyte α4 integrins found on monocytes and lymphocytes.[30] Binding between integrins on leukocytes and corresponding receptors on endothelial cells that form the BBB is necessary for monocytes and lymphocytes to enter the CNS.[30]

The antibody is effective for treatment of MS because it suppresses passage of these activated leukocytes from the blood stream into the brain (Figure **8–1**).[56] Two phase III trials have demonstrated efficacy of the drug in patients with RRMS.[57,58] One of these studies was a controlled trial of monotherapy with natalizumab versus placebo, while the other trial compared monotherapy with combination therapy of natalizumab with IFN-β1a. Both studies showed that patients taking natalizumab were more likely to remain relapse free, less likely to have sustained progression of disability, and less likely to acquire new gadolinium-enhancing lesions than controls. Natalizumab has also been shown to improve quality of life in patients with RRMS.[59] The drug was approved for treatment of RRMS by the FDA in 2004, but approval was suspended in 2005 after the appearance of progressive multifocal leukoencephalopathy (PML) in three patients.[60] After review of more than 3000 additional patients, the drug was re-released with a black box warning about PML in a restricted distribution and monitoring program.[61] Only patients with RRMS who have failed conventional therapy with IFN-βs or glatiramer should be considered for treatment with natalizumab.[48] Contraindications include hypersensitivity to the drug, impaired immunity or treatment with other immunosuppressive drugs such as mitoxantrone or cyclophosphamide in the previous three months. Allergic reactions as well as neutralizing antibodies have been reported in a small number of patients.[62–63] The drug is administered IV once a month in a dose of 300 mg in an infusion center and follow-up is prescribed under the TOUCH Prescribing Program. Pregnancy is not advisable during treatment because α4 integrins play a role in fetal development.[30]

Mitoxantrone

Mitoxantrone is a synthetic antineoplastic and immunosuppressive agent that reduces B-cells, inhibits T-cells, and prevents macrophages from degrading myelin.[64,65] It must be administered IV and has been shown to reduce clinical relapses and development of MRI lesions in patients with worsening RRMS, SPMS, or PRMS. It is generally reserved for patients unresponsive to other medications because of its cardiac toxicity and lifetime dose limitation of 140 mg/m^2.[65,66] Cardiac toxicity occurs in less than 2% of patients and is dose related.[67] The drug can cause severe decreases in left ventricular function, which should be monitored. Other side effects include nausea, alopecia, amenorrhea, leucopenia, and elevated liver enzymes. Occurrence of leukemia following treatment with this drug has also been reported.

Other immunosuppressive agents

Other immunosuppressive agents, especially azathioprine and cyclophamide, are used as off-label drugs for treatment of patients who do not respond to first-line immunomodulatory treatments for MS and related disorders including recurrent transverse myelitis and multiphasic ADEM.[48,67] These drugs act by reducing populations of activated inflammatory leukocytes that enter the CNS in MS. The use of azathioprine for treatment of RRMS and SPMS reportedly remains high in Europe as monotherapy or in combination with IFN-β.[67] Side effects include leukopenia, nausea, liver disease, and risk of cancer. Cyclophosphamide is another antineoplastic drug that has been used in a small number of studies for MS with conflicting results. It has been used primarily for patients with SPMS with rapid progression and continues to be used for a minority of patients, especially in France and the United States. Cyclosporine is an immunosuppressive agent used for organ transplantation that is being investigated for MS.[67] Other agents that have been used in small numbers of patients who are treatment failures with current approved therapies include methotrexate, mycophenolate, IV immunoglobulin, and other monoclonal antibodies including rituxumab, daclizumab, and alemtuzumab.[48]

Guidelines for disease modifying therapy of ms

Evidence-based guidelines for the use of DMTs in MS have been developed by several organizations including the American Academy of Neurology (AAN) and the National Multiple Sclerosis Society (NMSS) in the United States.[19,47,48,65,68] These guidelines recommend that treatment with one of the approved immunomodulators should be started as soon as possible after a definite diagnosis of MS is established. and should be considered in selected patients with a first attack (CIS) who have a high risk for developing MS. As described previously. short-term high dose therapy with intravenous methylprednisolone remains useful for hastening recovery from disabling relapses of MS, but this is not considered a DMT. Once DMT is started. it should be continuous and long term, and discontinued only if there is lack of benefit, significant side effects, or if better therapy becomes available. Most common medical conditions do not contraindicate therapy but these drugs should not be used in pregnant women or women trying to become pregnant.

Therapy is generally initiated with one of the IFN-βs chosen by an experienced clinician on a case-by-case basis. The AAN/NMSS guidelines indicate that there is strong evidence that IFN-β therapy reduces the relapse rate in MS and evidence that it probably also reduces long term disability and MRI lesions.[48] Efficacy as well as the convenience of administration (daily injections versus once a week) and side effects such as flu-like symptoms play a role in the choice of IFN-β preparations for individual patients. Patients receiving IFN-βs should be followed regularly every three months for the first year then every six months with examinations and complete blood count (CBC) and liver function tests, and thyroid stimulating hormone is checked annually. There is no recommendation at this time for checking NAbs for interferons.

Glatiramer acetate is generally used for patients who have failed therapy with interferons. It has a good side-effect profile and does not cause NAbs, but its onset of action is delayed compared to other therapies. The AAN/NMSS evaluation found strong published evidence that it reduces relapses, but evidence supporting its effect on new MRI lesions and disability is weaker, supporting a rating of “possibly effective” for these end points.[48] In contrast, the effectiveness of natalizumab for reducing relapse rate, new MRI lesions, and disability in patients with RRMS was rated as “established” based on the literature.[48] However, this drug is reserved for patients who do not respond well to other immunomodulators because of its side effects and risk of PML, and access is restricted by the FDA as described previously. Natalizumab is not used for patients with PPMS at this time as their pathology appears to be different from those with RRMS. Mitoxantrone also appears to be an effective immunosuppressive drug for MS, but it should also be reserved for patients with worsening RRMS or SPMS not responding to approved therapies because of its cardiac toxicity and lifetime limited dose.[66] The AAN/NMSS evaluation found evidence that mitoxantrone is probably effective for reducing attacks and possibly effective for reducing disability, but did not find evidence on MRI lesions. Immunosuppressive therapies including azathioprine and cyclophosphamide should generally not be used as first-line therapy for the relapsing forms of MS, but can be useful in selected patients with clinical subtypes of MS or related demyelinating disorders without accepted treatments.

Conclusion

Multiple sclerosis and related immune mediated demyelinating disorders are common neurological disorders. Corticosteroids are useful for producing short-term improvement but lack the ability to modify the course of MS. However, the advent of disease modifying drugs for MS has greatly improved the lives of many people with over the last decade, allowing them to live with fewer relapses and reduced long-term disability. An understanding of the unique mechanisms of these drugs has developed along with knowledge about pathogenesis of MS. The IFN-βs work by shifting T-cells and monocytes from an inflammatory to antiinflammatory program while glatiramer acetate competes with myelin antigens in antigen presentation cells and activates anti-inflammatory Th2 helper T-cells. In contrast, the action of natalizumab is focused on blocking integrin mediated passage of activated monocytes and T-cells through the endothelium of the the BBB. Natalizumab demonstrates the power of humanized monoclonal antibody therapy in MS, but also illustrates that modulating the immune system can be a double-edged sword allowing the emergence of virus-causing PML. Mitoxantrone inhibits T-cells, macrophages, and B-cells, but its usefulness is limited by cardiac and other side effects. Despite progress in this area, there is great need for new therapies for patients who have failed to respond to current medications and better ways to deliver these medications orally to improve compliance.[69]

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Spasticity in Spinal Cord Disorders

Chapter: Spasticity in Spinal Cord Disorders
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Care of patients with spinal cord dysfunction caused by trauma, multiple sclerosis, transverse myelitis, infections, and other acquired and degenerative diseases is common in the practice of neurology. The clinical presentations of all these disorders are dominated by spasticity, which is a major cause of pain and disability. The therapies available to the clinician to manage spasticity have expanded substantially over the past half-century, particularly in the past two decades. In this chapter, we provide an overview of the rationale and recommendations for current treatment options, based on a balance of anatomy, physiology, pathophysiology, pharmacology, clinical practice guidelines, as well as stem cell and regeneration research.

The problem spinal cord injury

After the initial spinal cord trauma, central cord venous ischemic injury progresses rapidly. Eventually, the central cord is replaced by a fluid-filled cyst surrounded by a variable donutlike outer rim of white matter at the injury epicenter (Figure **9–1**).[1] Within the remaining tissue at the injury level as well as for several segments above and below the injury a more subtle pattern of secondary injury occurs based on cellular factors of selective vulnerability leaving a gradient of pan-cellular loss to very refined selective cell loss. For example, interneurons that contain γ-aminobutyric acid (GABAergic) are one of the most vulnerable types of neurons to the factors of secondary injury.[2] The selective loss of GABAergic interneurons is one large component leading to the phenomena of disinhibition following spinal cord injury (SCI) and a major factor contributing to development of spasticity.

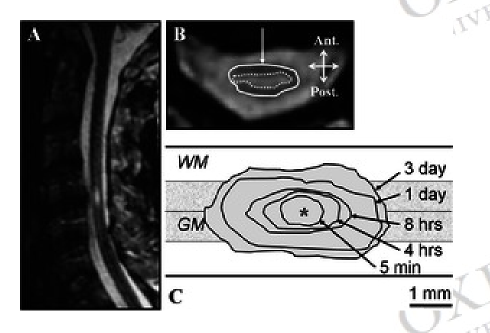




Figure 9—1.
Cervical spinal cord injury. (A) (B) Sagital and axial MRI images of chronic injury. (C) Secondary injury.

The severity of SCI and levels of paralysis are classified using the American Spinal Injury Association (ASIA) scale (Table 9–1). More than 60% of traumatic injuries in the United States are graded as ASIA A *(complete)*. Reported outcomes for SCI, particularly ASIA A class are poor (Table 9–2). Fewer than 3% recover the ability of walking and less than 10% regain substantial sensory function to be reclassified as ASIA B-D *(incomplete)*. For several reasons, spasticity is often a more challenging and impairing

problem with the more incomplete SCIs, particularly ASIA D classification. It is in this class where implementation of baclofen pumps are frequently necessary and where it is easiest to demonstrate that careful titration of antispasticity treatment *improves* function such as gait.

Table 9–1 ASIA Impairment Scale

Grade	Description
A	Complete. No sensory or motor function preserved in the sacral segments S4–S5.
B	Incomplete. Sensory but not motor function preserved below the neurologic level and extending through the sacral segment S4–S5.
C	Incomplete. Motor function preserved below the neurologic level; majority of key muscle have a grade < 3.
D	Incomplete. Motor function preserved below the neurologic level; majority of key muscles have a grade >3.
E	Normal motor and sensory function.

Table 9–2 Summary of Recovery in ASIA A-D Patients

ASIA A

1. Most (60%—90%) regain one motor level.
2. 0% to 11% will improve one or more ASIA grades.
3. 4% to 10% may undergo late conversion (after 30 days) to ASIA B or better. This can occur up to 2.5 years after injury.
4. Most motor recovery occurs during the first six months after injury, with the greatest rate of change during the initial three months. Motor strength can continue to improve during the second year.
5. Muscles graded 1–3 in the zone of partial preservation (ZPP) will recover useful motor function.

See McDonald for reference details.[42]

Long-term disability from SCI results not only from the initial loss of function but also from the complications that accumulate. Up to 30% of individuals with SCI are hospitalized every year for complications[3] such as infections (lung, skin, bowel, bone, and urinary tract), osteoporosis and pathologic bone fractures, autonomic dysreflexia, and heterotropic ossification.[4,5] Muscle wasting is a major sequelae resulting from disuse and from the absence of nerve impulses, which are critical for maintaining junctions between nerves and muscles.[6,7] Severe spasticity is common to almost all ASIA grades and levels of SCI. The exception is multilevel cervical and cauda-equina lesions that result in loss of segmental motorneurons and substantial lower motor neuron signs. Such spasticity can interfere with activities of daily living (ADLs), attendant care, and sleep and can impair motor control function. As a result, antispasticity treatment, particularly first-line GABAergic drugs (e.g., Baclofen), is initiated in most individuals with SCI during the acute rehabilitative phase of recovery and treatment is generally continued life-long.

An understanding of the pathogenesis of SCI, concepts of selective cell vulnerability to secondary injury, and development of longterm complications is important since all these factors play an important role in formulating strategies of treatment as they all contribute to development and/or manifestation of spasticity.

Mechanisms of spinal cord injury and changing treatment goals

Primary Injury

Traumatic injury occurs when broken fragments of bone and ligament impinge on the soft spinal cord. The cord responds by swelling until it encounters resistance from the bony canal of the spinal column. The swelling that compounds the initial injury reduces venous blood flow, causing a secondary venous infarct in the central part of the cord. This initiates a cascade of events that injures neighboring tissue. During this secondary phase, which occurs in the first 24 hours after the primary phase, cells die by excitotoxic necrosis as well as by apoptosis. This causes the initial injury site to rapidly enlarge into a hole in the middle of the spinal cord (Figure **9–1C**). Because a donutlike rim of viable tissue usually remains at the level of injury, SCI affects preferentially gray matter with variable and more selective injury of cellular elements in the surrounding white matter.

Second Temporal Wave Cell Death

A second wave of delayed cell death occurs during the weeks after a SCI.[8] It removes mostly oligodendrocytes, the myelinating cells, from adjacent white matter tracts. Since each oligodendrocyte myelinates 10 to 40 different axons, loss of one oligodendrocyte leads to exponential loss of myelin and therefore functions as far as five levels above and below the injury epicenter. The problem does not stop with the secondary wave of cell death, however. An injured, under active nervous system may be unable to adequately replace cells, particularly glial cells that normally turn over.[9] Therefore, individuals with SCI may experience a slow, progressive loss of neurological function over long periods in addition to complications from their initial injury. It is important to consider this potential for further loss of function when determining the treatment algorithm for spasticity, since most of these approaches work by enhancing inhibitory circuitry thereby reducing overall neural activity, which may interact negatively with spontaneous recovery and strategies to enhance spontaneous regeneration.

Goals of restoration

Despite the poor outcomes for most patients with SCI, occasional individuals have regained near-normal function. Figures **9–1A** and **9–1B** show the spinal cord of a man who was injured at C4–5 more than 20 years ago. He lost more than two thirds of the central spinal cord including substantial damage of ascending and descending axons. Despite these deficits, he can now compete in Iron Man triathlons.[1,10] This case demonstrates an important concept: *it is not necessary to cure SCI to restore function; partial repair can suffice*. Thus, small anatomical gains can translate into disproportionate gains in function. This observation is compatible with experimental SCI models that have shown: (1) 10%–15% of functioning connections across the lesion level is sufficient to allow walking;[9] (2) major injury from SCI trauma, tumor resection, palliative cord hemisection, and hemispherectomies is compatible with recovery of pragmatic function; (3) segmental and intersegmental circuitry remains intact both above and below the injury level; and (4) the presence of central pattern generators (CPGs) in the lumbosacral and cervical spinal cord act as mini-computers that require only limited descending tract control as well as segmental sensory input to the spinal cord to control walking and some arm functions.

Pathophysiology of spasticity

Spasticity is defined as a motor disorder characterized as a velocity-dependent increase in muscle tone with exaggerated reflex responses resulting from hyperactivity of the

tonic stretch reflex and exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex. Clinically, it consists of positive and negative symptoms. Positive symptoms include: spasms, dystonia, exaggerated cutaneous reflexes, autonomic hyper-reflexia, and a set of long-term consequences including contractures. Negative symptoms include paresis, loss of fine motor movements, and fatigability.

Mechanisms for Spasticity

Spasticity can be a consequence of either decreased inhibition or increased excitability within the neuronal circuits that control muscle tone in the spinal cord (Figure **9–2**). Decreased inhibition can occur in the presynaptic inhibition loop, disynaptic reciprocal Ia, nonreciprocal Ib or group II inhibition. More research to date has supported deficient presynaptic and nonreciprocal inhibition and alpha motor neuron hyper-excitability rather than deficient group II afferents or Renshaw inhibition.[12–14]

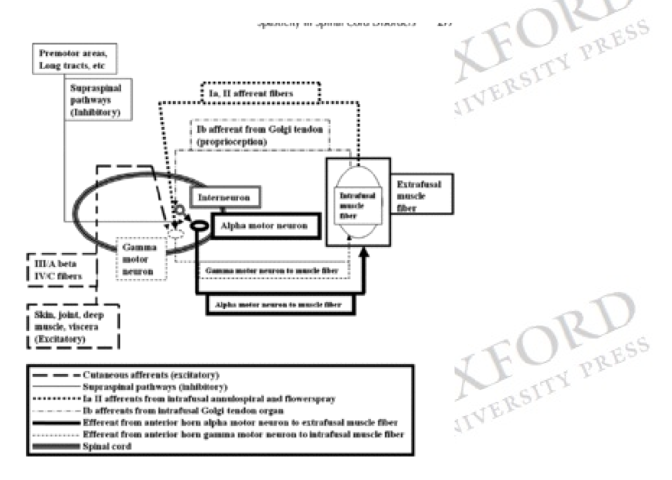




Figure 9–2.
Neural pathways involved in spasticity.

The circuits in the spinal cord that control muscle tone are responsible for three major reflexes that are enhanced in patients with spasticity: the muscle stretch reflex, the Golgi tendon organ reflex, and the flexor withdrawal reflex.[15] *The muscle stretch reflex* is triggered by active lengthening of the muscle fiber. Afferent impulses are carried through Ia and II type fibers to the alpha motor neurons in the anterior horn and, through direct monosynaptic excitation, produce contraction of the stretched muscle and its synergists (Table 9–3). The same afferent impulse produces disynaptic inhibition (through inhibitory interneurons) of the antagonist muscles, resulting in relaxation of antagonist muscles. In contrast, the *Golgi tendon organ reflex* is mediated by the Golgi tendon organ, which is sensitive to active muscle contraction and tension and transmits rnformation through myelinated Ib fibers. Stimulation of Ib afferents leads to inhibition of the agonist alpha motor neuron and its synergists and to excitation of antagonistic alpha motor neurons (inverse myotatic reflex/Ib nonreciprocal inhibition), in a rhythmic manner in some instances (e.g., part of the spinal rhythm generator for locomotion). The *flexor withdrawal reflex* differs from these two reflexes because it is triggered by nociceptive stimuli. Afferent fibers are known collectively as flexor reflex afferents (FRA), usually group III and IV afferents from skin and deep muscle (Table 9–3). Activation of FRAs produces excitation of posterior horn neurons. These, in turn, activate interneurons in the anterior horn that excite ipsilateral flexor motor neurons and inhibit ipsilateral extensor motorneurons. Through commissural neurons activation, contralateral extensor motor neuron activation and contralateral flexor motor neuron inhibition occurs.

Table 9–3 Nerve Fiber Classification

Fiber type (Loyd and Hunt)	Fiber Type (Erlanger and Gasser)	Fiber size (micrometers)	Velocity (m/s)	Function
Ia	A alpha	10–20	50–120	Motor: alpha motor neurons to extrafusal muscle fibers Sensory: annulospiral endings from muscle spindle (proprioception)
Ib	A alpha	10–20	50–120	Sensory: Golgi tendon organs (proprioception, pressure, deep touch)
II	A beta	4–12	25–70	Motor: intrafusal and extrafusal muscle fibers Sensory: flowerspray endings from muscle spindle (proprioception); pacinian and paciniform corpuscles (pressure)
III	A gamma A delta	2–8 1–5	10–50 3–30	Motor: gamma motor neurons to intrafusal muscle fibers Sensory: free nerve endings and some specialized endings (pain, touch, temperature)
IV	B C	1–3 <1	3–15 <2	Motor: preganglionic autonomic fibers Motor: postganglionic autonomic fibers Sensory: free nerve endings, unmyelinated (pain, temperature)

Major Targets for Therapy

The major targets for pharmacotherapy within the circuits described previously include components in the muscle itself, the cutaneous afferents entering the dorsal root ganglion, the dorsal root ganglion itself, and neurons within the dorsal and ventral horns of the spinal cord gray matter (Figure **9–2**).

Muscle spindle

The muscle spindle contains two types of muscle fibers: nuclear bag fibers (dynamic and static) and nuclear chain fibers (Table 9–3). Dynamic nuclear bag fibers are sensitive to the rate of change of the muscle length (phasic); static nuclear bag fibers and nuclear chain fibers are sensitive to the steady-state muscle length (tonic, static). Two types of myelinated sensory afferent nerve fibers transmit the information from the nuclear bag and nuclear chain fibers: type Ia transmit both phasic and tonic stretch

information; type II transmit tonic stretch information. The Golgi tendon organ is an encapsulated receptor located in the tendon, close to the tendon/muscle junction. Each organ is innervated by a single Ib fiber that forms a spray-like ending in contact with the tendon fascicles. Tension produced by active muscle contraction stimulates the Ib fibers better than tension produced by passive muscle stretch.

Cutaneous afferents: fibers iii/a beta and iv/c

Type III/A beta fibers carry information related to pain from free and specialized endings in muscle and joints; information related to sharp pain, heat, cold, touch, and pressure from skin; and information from visceral afferents. Type IV/C fibers are small diameter sensory fibers that traditionally carry poorly localized pain/nociceptive information and thermoregulatory functions from skin, deep muscle, and viscera.

Dorsal horn and root ganglia

The dorsal horn and root ganglia houses the cell body for the nociceptive afferent fibers that are part of the flexor withdrawal reflex. These neurons activate the interneurons in the anterior horn that excite flexor motor neurons and inhibit extensor motor neurons ipsilateral to the stimulus.

Inhibitory neurons release GABA to modulate the activity of the group Ia and II fibers (Table 9–3). They are activated suprasegmentally through the corticospinal and spinocere bellar tracts, mainly through GABA (presynaptic inhibition of Ia and II afferent pathways), but some are also activated through alpha adrenergic and amino acid neurotransmitters. Renshaw cells are special inhibitory interneurons that are activated by motor neuron collaterals and cause inhibition of motor neurons of same and synergistic muscles. They modulate activity of both the anterior horn cells and inhibitory interneurons through a negative feedback circuit.

Ventral horn

Alpha motor neuron activity is modulated through multiple mechanisms (presynaptic inhibition, postsynaptic depression, disynaptic reciprocal Ia inhibition, recurrent inhibition, Ib inhibition; Table 9–3). The neurons send fast efferent impulses (conduction velocities of 50–120 m/s) to the main extrafusal muscle fiber. Gama motor neurons send efferent impulses that control the intrafusal/fusimotor contractile elements that stiffen the region of the nuclear bag fibers in the muscle spindle, maintaining spindle sensitivity during skeletal muscle contraction. The fusimotor axons have conduction velocities of 10–50 m/s. No direct evidence exists for gamma system upregulation secondary to increased fusimotor (motor fibers) drive.

Drug therapy for spasticity

Challenges to Therapy for Spasticity

Optimized treatment is an ongoing challenge in all patients with SCI because the target fluctuates over time secondary to an array of factors including diurnal, environmental, and physiological variables. First, dysautonomia, a highly variable, unavoidable fact of spinal injury, acts as an overly responsive dysregulator of muscle tone and response to sensory input. Also, the degree of spasticity varies across functional muscle groups, often most prevalent in antigravity muscles. Spasticity is also affected by the level of injury, whether it is focal or multifocal, and whether is it is symmetrical or asymmetrical. Furthermore, the intermittent, stimulus-driven nature of spasticity makes assessment and optimal regulation difficult. The Ashworth scale is widely used as a clinical semiquantitative scale of spasticity (Table 9–4), and other quantitative methods such as dynamometry are also used commonly. However, a variety of other factors contribute to function, quality of life and ability to perform activities of daily living in patients with SCI. Measurement of these factors needs to be included in assessment of therapeutic interventions. Spasticity is a problem that involves both the motor and sensory systems, particularly their integration and summated responses. For example the spasticity syndrome also affects smooth muscle responses of the internal organs, including bowel and bladder. Another issue is the challenge of treating localized pathology in the spinal cord and neuromuscular system with systemic drug treatment. Advances in bioengineering allow for more focal drug delivery greatly improving their therapeutic effectiveness.

Table 9–4 Ashworth Scale

Score	Definition
Ashworth scale	
1	No increase in tone. Normal tone.
2	Slight increase in tone giving a “catch” when affected part is moved in flexion or extension.
3	More marked increase in tone, but affected part easily moved.
4	Considerable increase in tone; passive movement difficult.
5	Affected part rigid in flexion or extension.



The clinical treatment of spasticity in these disorders is important and optimal titration of spasticity rather than its elimination is the goal. Some spasticity is useful and contributes to functional abilities in individuals with SCI. Overtreatment of spasticity is all too common of practice. This trend, in part, is supported by the historical, largely implicit, assumption that pharmacological treatment of spasticity is relatively free of serious long-term consequences. However, recent discoveries in regeneration research clearly demonstrate the importance of caution and careful titration in treatment of spasticity with the cognizance for the propensity of most pharmacological spasticity treatment approaches to impair spontaneous regeneration and accelerate central nervous system (CNS) aging.

Systemic Changes That Affect Therapy

Individuals with SCI have substantial physiologic changes related to their injury. Spinal cord injury induces dysfunction of the autonomic nervous system, which in turn affects the absorption, distribution, metabolism, and excretion of the drugs. Spinal cord injury also results in metabolic changes that affect the general milieu of the SCI afflicted body. The dysfunction of the autonomic nervous system manifests as delayed gastric emptying, reduced gastrointestinal (GI) tract motility, impaired blood flow to tissues, abnormal blood pressure and body temperature regulation. Individuals with SCI can also have anemia, lower plasma protein levels, increased extracellular fluid, reduced lean body mass and impaired immune system activity compared with healthy individuals, and these conditions can affect drug pharmacokinetics.

For example, delayed gastric emptying of acidic drugs such as aspirin and acetaminophen can cause more rapid onset of their therapeutic effect in individuals with SCI. Conversely, the onset of basic drugs (i.e., codeine, meperidine) may be delayed. Reduced GI tract motility prolongs the contact of the drug with the small intestines’ large absorption area, increasing their bioavailability, but also exposes the drug to the contents of the gut for an increased period of time, allowing some to be destroyed by bacteria, hence reducing their bioavailability. Drugs that undergo eneterohepatic circulation (i.e., benzodiazepines) have significantly prolonged half-lives.

Impaired/decreased blood flow to tissues (skin, muscles, liver, and kidney) can decrease absorption and peak blood concentration, especially when drugs are administered in areas below injury level by transcutaneous, subcutaneous or intramuscular methods. Hepatic blood flow may be reduced, decreasing drug metabolism, and prolonging plasma half-life. Creatinine clearance and glomerular filtration rate are different than in normal population[16,17] and nomograms are available for SCI individuals. Abnormal blood pressure and temperature regulation can also influence all pharmacokinetic stages, from absorption to distribution, metabolism, and excretion.

Anemia and low plasma protein levels impair drug distribution and delivery to target organs, and fewer plasma protein binding sites means that more drug circulates freely, ready for tissue delivery, and potentially inducing toxicity at standard dosing. Increased extracellular fluid (edema) expands the drugs' volume of distribution, lowering blood concentration, and possibly negating the effect of low protein levels for certain drugs. There is also significant reduction in lean body mass following SCI induced paralysis.[18,19] The loss of lean tissue is expected to have profound implications on drug pharmacokinetics. All these changes require an individualized, carefully monitored pharmacologic approach for all individuals with SCI, much like for children, elderly, and individuals with hepatic or renal dysfunction.

Drugs used to treat spasticity

Drugs Acting Through GABAergic System

Major drugs used to treat spasticity in patients with SCI are summarized in Table 9–5.

Table 9–5 Options for Pharmacological Therapy of Spasticity

Medication	Brand	Mechanism of Action	Half Life	Protein Bound	Metabolism	Dosing
Baclofen	Lioresal	GABA B receptor agonist	5.5 h	30%	15% liver CYP450	20–140 mg/d orally divided twice a day or four times a day intrathecal start 50–100 meg
Diazepam	Valium	GABA A receptor agonist	30–100 h	98%–100%	liver CYP1A, CYP2C	2–40 mg/d orally divided twice a day or four times a day
Clonazepam	Klonopin	GABA A receptor agonist	20–50 h	85%	liver CYP3A	0.5–5 mg orally twice a day
Dantrolene	Dantrium	reduces calcium flux across sarcoplasmic reticulum in the skeletal muscle	4–8 h		liver CYP450	25–400 mg/d orally divided four times a day
Clonidine	Catapres	alpha 2 receptor agonist	12.7 h		liver CYP450	0.2–2.4 mg/d orally 0.1–0.3 mg/d transdermal patch
Tizanidine	Zanaflex	alpha 2 receptor agonist	2.5 h	30%	liver CYP1A2	2–36 mg/d orally divided twice a day or four times a day
Cyproheptadine		piperidine HI-antagonist	1–4 h		liver CYP450	4–16 mg/d divided twice a day
Dronabinol	Marinoi	endogenous cannabinoid receptor agonist	25–36 h	97%	liver CYP2C9	5–120 mg/d divided in 3–5 doses
Gabapentin	Neurontin	GABA agonist	5–7 h	<3%	none	100–3600 mg/d divided twice a day
Propranolol	Inderal	beta-adrenergic receptor antagonist	3–5 h	>90%	liver CYP1A2, 2C19, 2D6	40–640 mg/d divided twice a day or four times a day
Levodopa	Sinemet	dopamine precursor	0.75–1.5 h	—	kidney, GI tract	25/100mg tablets: 1–8 tablets per day divided twice a day

Baclofen is a GABA-B (bicuculline-insensitive) receptor agonist structurally similar to GABA. There are GABA-B receptors located both presynaptic and postsynaptic. Binding onto the presynaptic receptors restricts calcium influx producing hyperpolarization of the neural membrane and reduces endogenous release of the excitatory neurotransmitter glutamate. Binding onto the postsynaptic receptors of the la sensory afferent terminals increases potassium conductance, producing membrane hyperpolarization at this level, with subsequent reduced excitability of the primary afferent terminal. Presynaptic inhibition is thus increased, resulting in further decrease of neurotransmitter release. Reduced release of glutamate from dorsal root afferents caused by baclofen resembles the effect produced more permanently by surgical dorsal rhizotomy.

Baclofen activation of GABA-B receptors causes inhibition of gamma motor neuron activity, reduced drive to intrafusal muscle fibers and reduced muscle spindle activity,[20] inhibiting monosynaptic and, to a lesser extent, polysynaptic spinal reflexes.

Baclofen can be administered orally or intrathecal. After oral administration, it is rapidly absorbed in the upper GI tract. Absorption is dose-dependent, being reduced with increasing dose. The distribution volume is approximately 2.4 L/kg and lt 30% is bound to plasma proteins. Only 15% of the dose is metabolized in the liver, the rest of it being excreted unchanged in the urine. Therapeutic half-life ranges from 2–6 hours (mean 3.5 hours). Dosing may start at 5 mg, 1–4 times/day and increased gradually to a therapeutic level. The recommended maximum dosage is 80 mg daily divided and four doses, but clinical higher dose usage (80–140 mg) is common.[21] Reported common side effects are sedation, muscle weakness, respiratory compromise. Seizures (including status epilepticus after intrathecal drug administration) and loss of seizure control has also been reported during treatment with oral baclofen. Abrupt baclofen withdrawal may produce confusion, hallucinations, seizures, rebound spasticity, and fever. Intrathecal administration results in a marked increase in potency compared with oral baclofen. Following an intrathecal Baclofen (Lioresal) bolus dose, the onset of action is 0.5–1 hour. Peak spasmolytic effect is seen at approximately four hours after dosing and effects may last four to eight hours. Following continuous infusion, antispastic action is first seen at 6–8 hours after dosage change initiation. Maximum activity is observed in 24–48 hours. The pharmacokinetics of CSF clearance of intrathecal baclofen, calculated from either intrathecal bolus or continuous infusion studies approximates CSF turnover, suggesting elimination is by bulk flow removal of CSF. After a 50 or 100 mcg lumbar bolus

injection, the average CSF elimination half-life was 1.51 hours over the first four hours and the average CSF clearance was 30 mL/hour. Concurrent plasma concentration of baclofen during intrathecal administration is expected to be very low (0–10 ng/mL). There is a 4:1 lumbar:cisternal gradient of the drug along the neuroaxis and the gradient is reportedly not altered by body position.

Dosing is established by performing a preimplantation trial. A bolus injection (50 μg) by single lumbar puncture or temporary catheter insertion is administered. The muscle tone is evaluated before trial and over the next 4–6 hours after the drug administration. A one point decrease in Ashworth score (Table 9–4) is considered a positive response. If the 50 μg bolus is not effective, then trials with 75 or 100 μg could be conducted on following successive days until a therapeutic response is obtained. A successful trial is followed by implantation of a delivery system (Medtronic SynchroMed II and SynchroMed EL Programmable Drug Infusion Pump, Minneapolis). The implantation involves an invasive procedure performed in the operating room and consisting of subcutaneous pump implantation into an abdominal skin pocket and threading of the delivery catheter from the pump to the intrathecal space. The location where the catheter enters the intrathecal space is usually at or below T8 level (to avoid respiratory compromise), but more recently threading the catheter at cervical level has been done successfully, optimizing the effect of the drug onto upper extremities, trunk and lower extremities muscles.[22] The drug can be delivered through continuous infusion and timed boluses can also be programmed. Periodic refill of the pump is done in an office setting using sterile technique.

Benzodiazepines

Benzodiazepines are GABA-A agonists that act by opening chloride channels at the presynaptic membrane level, hyperpolarizing the neural membrane and blocking action potentials and, thus preventing release of neurotransmitter from the nerve terminal. Diazepam is absorbed quickly after oral administration, and peak blood level occurs in one hour. Distribution volume is high as the drug is highly lipid soluble, and it is 98%–100% bound to plasma proteins. Most of the drug is metabolized in the liver (CYP1A, CYP2C) to an active compound N-desmethyldiazepam, and very little is excreted unchanged in the urine. The half-life is 20–80 hours, when metabolites are included. Usual starting dose is 2–5 mg at nighttime or 2 mg during daytime. The dose can be titrated to effect and administered 1–3 times/day. Common side effects are somnolence, tiredness, and sedation. Symptoms of withdrawal include anxiety, agitation, restlessness, tremor, irritability, muscle fasciculation/twitching, nausea, hypersensitivity to touch, smell, sound, and taste, as well as insomnia, nightmares, seizures, hyperpyrexia, psychosis and death. Symptoms of withdrawal are more common if the drug is used chronically (i.e., eight months). Withdrawal symptoms can persist for up to six months even when the drug is withdrawn slowly, over weeks.

Clonazepam can also be used orally for spasticity in patients with SCI. Absorption occurs rapidly in the stomach and peak blood levels occur in one to two hours after oral administration. Distribution volume is high because of lipophilicity, and it is 85% bound to plasma proteins. It is metabolized in the liver (cytochrome P3A) with a half-life of 18–28 hours. Usual starting dose is 0.5 mg at nighttime, used to suppress spasms that disturb sleep.

Possible Adverse Effects of Excessive GABAergic Therapies

Experimental data suggests that an optimal level of neural activity in the injured spinal cord is desirable to promote optimal recovery (see further on in this chapter). Accordingly, we recommend limiting therapy with baclofen or benzodiazepines to the lowest doses possible. Our experience indicates that it is feasible to limit therapy to a single GABAergic drug in more than 90% of patients. In addition we have been able to discontinue baclofen therapy in almost half our patients and reduce the dose to less than 30 mg per day in the most of them. Success is optimal when titration is very slow and combined temporally with optimized levels of physical activity or activity-based restoration therapies for those more severely mobility impaired. Some spasticity is beneficial and therefore, treatment goals of spasticity should be aimed at amelioration of severe spasms that impair activities of daily living or substantially interfere with other aspects of life and rehabilitation treatment. Treatment should begin with optimization of physical activity, systemic assessment, and elimination of offending triggers of spasticity (i.e., kidney/bladder stones, esophageal or gastro-duodenal ulcers, reactive airway disease, colonic obstruction), neurological assessment, and brain imaging to rule out treatable structural causes of worsening spasticity such as syringomyelia, tethering, spinal stenosis, foramina narrowing, or disc protrusion. Focal pharmacological treatments such as botulinum toxin are often successful in reducing trigger muscles or spasticity propogation, and limited application of polypharmacotherapy is sometimes warranted and effective.

Drugs affecting ion channels

Dantrolene is a hydantoin that reduces calcium flux across sarcoplasmic reticulum in the skeletal muscle, both fast and slow fibers. This uncouples motor nerve excitation and skeletal muscle contraction. It direct action on muscle means that it tends to produce less sedation than centrally active drugs, and can be combined with other drugs like benzodiazepines. A disadvantage of danrolene is its tendency to produce muscle weakness at higher doses. It can be administered orally or intravenously, and absorption of the oral dose (a hydrated sodium salt) occurs in the small intestine. Peak blood concentration of the free acid, dantrolene, occurs in three to six hours; peak blood concentration of the active metabolite, 5-hydroxydantrolene, occurs in four to eight hours. Being lipophilic, it has a wide volume of distribution (0.54 1/kg in children).[23] It is metabolized in the liver by microsomal enzymes to the active 5-hydroxydantrolene, and the half-life of the oral dose is 8.7 hours after a 100 mg oral dose. It is excreted in the urine 15%–25% unchanged, with the rest as metabolites. Usual starting dose is 25 mg once daily, increasing by 25 mg every four to seven days, to a dose of 100 mg four times/day. Common side effects are drowsiness, dizziness, weakness, general malaise, and diarrhea. Toxicity manifests as hepatotoxicity, especially in patient receiving the drug over two months (1.8%) and periodic monitoring of liver function tests is indicated in individuals taking the drug chronically. Dantrolene has also been used to treat malignant hyperthermia, neuroleptic malignant syndrome, and hyperthermia following abrupt baclofen withdrawal.

Another ion channel blocker that is showing promise for spasticity in clinical trials is fampridine. This drug, also known by its chemical name of 4-aminopyridine, is a specific blocker of voltage dependent neuronal potassium and sodium channels. A recent phase II double-blind randomized placebo-controlled trial of this drug in patients with chronic spinal cord injury showed improvement in a subject global impression scale. A similar phase III trial in multiple sclerosis also showed improvement in spasticity. Fampridine may act by enhancing conduction in axons with impaired myelination in the partially injured tracts within the peripheral rim of white matter in the injured spinal cord. This may reduce spasticity by enhancing descending inhibitory suprasegmental signals.

Drugs that affect noradrenergic receptors

Clonidine is an alpha-2 adrenergic agonist that can act in the spinal cord to produce inhibition of the short-latency alpha-motor neuron response to group II muscle afferent stimulation, possibly by augmenting presynaptic inhibition. Clonidine also lowers blood pressure via alpha-2 mediated inhibition of locus coeruleus neurons, with subsequent decrease in tonic facilitation on sympathetic preganglionic fibers. It is administered orally or transcutaneously, and after oral administration, clonidine is absorbed in the small intestine and peak blood level occurs in three to five hours. Clonidine is highly lipid soluble and distributes widely throughout the body tissues, including the CNS. It is 95% bioavailable, being modestly bound to plasma proteins, and 50% of the absorbed dose is metabolized in the liver and half-life is 5–19 hours. Approximately half is excreted unchanged in the urine. Usual oral starting dose is 0.1 mg twice daily and can be increased weekly to a maximum of 2.4 mg daily (this large dose is rarely used). The transdermal patch comes in 0.1, 0.2, and 0.3mg/day patch form, delivered over seven days. Oral clonidine is also used in individuals with SCI for treatment of symptomatic autonomic dysreflexia with elevated blood pressure. Several studies have reported improvement in gait parameters of individuals with SCI using clonidine 0.2 mg/day dose.[24,25] Common side effects are weakness/fatigue, orthostatic hypotension, palpitations, and tachycardia/bradycardia. Toxicity/overdose manifests as CNS depression, early hypertension followed by hypotension, bradycardia, respiratory depression, hypothermia, and myosis.

Tizanidine is an imidazoline derivative that binds to spinal and supraspinal alpha-2 adrenergic and imidazoline receptor sites. It decreases polysynaptic reflex activity by restoring or even enhancing noradrenergic presynaptic inhibition, and it has been shown to facilitate the vibratory inhibition of the H-reflex. Its structure is similar to clonidine but it has less effect on blood pressure and causes less sedation. It is administered orally as tablet or capsule, and it is well absorbed in the small intestine. Peak blood level occurs in 1 hour. Food increases the peak plasma concentration of the tablets by about 30%, but decreases the peak plasma concentration of the capsules by 20%. Food delays the time to peak concentration for tablets by approximately 25 minutes and for capsules by two to three hours. As a result, capsules taken with food have a smoother plasma level, predisposing to fewer side effects and insuring a more homogenous effect on muscle tone. Tizanidine is widely distributed throughout the body, and it is 40%

bioavailable, being bound to plasma proteins about 30%. It is metabolized extensively in the liver with significant first-pass hepatic metabolism, and the half-life is two hours. The usual starting dose is two to four mg at night time, increased every two to four days to a maximum dose of 36 mg daily divided in three to four doses. Common side effects are weakness, fatigue, dry mouth, sedation/somnolence, and dizziness. Toxicity is manifested as hypotension, severe sedation, liver injury, and hallucinations. Of note, coadministration of ciprofloxacin, frequently used to treat urinary tract infections in individuals with SCI, significantly raises the tizanidine plasma concentration and pharmacologic effects.

Cyproheptadine is an older agent with activity as a piperidine H1-antagonist that acts at a number of transmitter sites, including serotonin, histamine, and acetylcholine. Perhaps its most profound effect is inhibition of the serotonin system. Cyproheptadine has been shown to decrease clonus and improve gait in a population with spasticity of various spinal origins. It is administered orally and has moderate solubility. Peak concentration of cyproheptadine occurs in about six to nine hours, and the duration of action is up to 10 hours. The drug is extensively metabolized in the liver, with only some unchanged drug excreted in feces. Plasma half-life ranges from one to four hours, and the drug is mainly excreted in it's conjugated forms through the kidneys. Dosage is usually started as 4 mg at night to avoid excessive sedation and dose should be increased every five days to a maximum of 16 mg. Most common side effects are CNS depression and dry mouth. Toxicity manifests as extreme sedation, liver toxicity, tachycardia, cardiac arrhythmia, and hypotension. Cyproheptadine has also been used to treat baclofen withdrawal symptoms, vascular headaches and to improve appetite.

Cannabinoids

Dronabinol is a synthetic oral preparation of delta-9-tetrahydrocannabinol (delta-9-THC), one of 66 active compounds, called cannabinoids, found in marijuana. Dronabinol was found to significantly decrease spasms and spasticity in individuals with SCI.[26] Dronabinol acts as an agonist at endogenous cannabinoid receptors, including CB1 and CB2. Cannabinoid receptors exert signal transduction effects through G-protein-coupled receptors, resulting in decreased excitability of neurons, and some reports suggest that cannabinoids can also stimulate adenyl cyclase. Dronabinol is absorbed well after oral administration, but it is highly lipophilic and undergoes extensive first-pass metabolism in the liver so that only 10%–20% of the administered dose reaches the systemic circulation. It has a very large volume of distribution (10 L/kg), and its metabolites are extensively protein bound (97%). Metabolism is by microsomal hydroxylation utilizing the CYP system. The elimination is biphasic, with a short half-life of four hours and a terminal half-life of about 25–30 hours. After oral administration, onset of action occurs at 0.5–1 hour and peak effect at two to four hours. The duration of psychoactive effects is four to six hours, but the appetite stimulant effect may continue for up to 24 hours after administration. Because of its large volume of distribution, dronabinol and its metabolites may be excreted at low levels for prolonged periods of time (more than five weeks in the urine and feces following single dose administration). Starting dose for spasticity management is 5–10 mg and the dose can be titrated upward to clinical effect by 2.5 to 5 mg every two to three days, divided in three to five doses, to a high of 120 mg daily (average 30 mg daily). Common side effects are dizziness, euphoria, dysphoria, irritability, paranoia, drowsiness, impaired cognition and fatigue. Tolerance to CNS side effects can appear as early as two weeks. Younger patients, especially those who have smoked marijuana, are more tolerant of these effects. Toxicity manifests as decreased motor coordination, lethargy, slurred speech, postural hypotension, seizures, and respiratory depression. An abstinence syndrome has been reported after the abrupt discontinuation of dronabinol manifested as irritability, insomnia and restlessness. Withdrawal symptoms manifest at 24 hours as sweating, hot flashes, rhinorhea, loose stools, hiccoughs, and anorexia. Symptoms dissipated over the next 48 hours. Disturbed sleep for several weeks following discontinuation of high dose dronabinol has been reported. Dronabinol is used as an antiemetic and as appetite stimulant.

Gabapentin

Gabapentin was designed as a GABA agonist but the exact mechanism by which it exerts its spasmolytic activity is not known. It is presumed to exert presynaptic inhibition of release from sensory nerve terminals, possibly by inhibiting voltage gated calcium channels. Gabapentin was found to decrease impairment of spasticity in individuals with multiple sclerosis as measured by the self-report scales of spasm severity scale, interference with function scale, painful spasm scale, and global assessment scale and by the physician-administered scales of the Modified Ashworth and plantar stimulation response.[27,28] Gabapentin was also found to decrease spasticity as assessed by Ashworth and Likert scales in 25 patients with SCI.[25] Gabapentin is administered orally and is rapidly absorbed, in part by the L-amino acid transport system. It is highly lipophilic, so it is distributed quickly to the CNS. Gabapentin is not metabolized and the drug is excreted intact in the urine. The elimination half-life ranges from five to seven hours (4.7 hours in children) and is significantly prolonged (52 hours) in adult patients with renal impairment (creatinine clearance <30 mL/min). Gabapentin is removed from plasma by dialysis. Starting dose is 100 mg titrated to clinical effect up to 3,600mg/day. Common side effects following gabapentin therapy are somnolence, dizziness, ataxia, fatigue, nystagmus, tremor, weight gain, nervousness/irritability, dysarthria, amnesia, back pain, and peripheral edema. Hepatitis has been reported rarely in pediatric clinical trials. Toxicity manifests as CNS depression.

Beta-adrenergic blockers

Propranolol has been found to depress clonus associated with spasticity. The drug exerts its action on the spinal cord but does not influence dynamic spindle activity or alphamotoneuron activity. It may disinhibit the tonic stretch reflex.[29] After oral administration of immediate-release propranolol, the dose is almost completely absorbed in the stomach. The drug is highly lipophilic and, as a result, is widely distributed throughout the body. It readily crosses the blood brain barrier (BBB) into CNS, and is greater than 90% bound to plasma proteins, primarily albumin. It is extensively metabolized upon first pass through the liver, the extent of metabolism being dependent on liver blood flow. A pharmacologically active metabolite, 4-hydroxypropranolol, is produced with the initiation of oral therapy, but it is eliminated faster than the parent drug. It is important to know that there are differences in the ability to metabolize propranolol among ethnic groups, which can affect efficacy and development of side effects and toxicity. Excretion of propranolol occurs renally, primarily as metabolites, with only 1%–4% of a dose excreted fecally as unchanged drug. Peak concentrations are achieved within 60–90 minutes after single dose administration. The elimination half-life of propranolol ranges from two to six hours, with chronic administration yielding longer half-lives, possibly due to saturation of liver binding sites and/or systemic clearance. In patients with severe renal dysfunction, fecal elimination can increase to compensate for decreased renal excretory processes. Propranolol is not appreciably removed by hemodialysis. Usual starting dose is 20 mg twice daily, dose that can be increased every three to seven days, up to a maximum of 640 mg daily (although this dose is never reached in the treatment of spasticity). Careful monitoring of heart rate and blood pressure is imperious, as the drug can induce bradycardia and hypotension. Possible side effects are dizziness, fatigue, depression, nightmares, hallucinations, diarrhea, nausea, myalgia, sexual dysfunction, and agranulocytosis. Toxicity manifests by bradycardia, heart block, hypotension, and cardiovascular collapse.

Focal or localized therapies: phenol and ethanol neurolysis

Phenol and ethanol have been used for years to accomplish chemical neurolysis to reduce spasticity. They act by denaturing the protein components of nerve fibers with resultant sclerosis. Both drugs can be injected into the peripheral nerve or the motor point of the muscle of interest or intrathecally. At lower concentrations (20%–40% for alcohol and 1% for phenol), they produce a local anesthetic effect followed by partial or total protein denaturation, depending on the concentration. At the therapeutic concentration, they produce denervation and at high doses and exposure time they produce tissue necrosis. The duration of action for these agents is variable, between 1–36 months,[30] with a clinically accepted average of six months.

Alcohol has been used to manage spasticity in cerebral palsy, stroke, multiple sclerosis, SCI and progressive multifocal leukoencephalopathy since early 1900's, but is rarely used now. Concentrations of 45%–65% have been used, injected intramuscularly (technique called intramuscular wash) or perineurally. Taylor described progressive histological changes according to the concentration of alcohol and exposure time in the mouse animal model.[31] An immediate splitting of myelin sheaths and swelling of cellular organelles and cytoplasm, followed by Wallerian degeneration and finally by muscle necrosis occurred. The authors noted that the alcohol dispersed rapidly from the injection site. Up to 10 mL of diluted alcohol (45%–65%) is injected after nerve localization utilizing nerve stimulation +/— fluoroscopy. Possible complications are short lasting injection site pain, long lasting deafferentation/ dysesthetic pain, phlebitis, nerve injury, and skin ulcerations. Marked reduction in motor strength has not been reported with alcohol neurolysis.[32,33] Alcohol has also been administered intrathecal for management of spasticity, but concerns regarding caudal migration of agent, motor weakness and systemic side effects were raised.[34–36]

Phenol is a benzene metabolite (benzyl alcohol) used in clinical management of spasticity in aqueous solution of 3%–5%. At low concentrations (0.2–2%), phenol has mainly an anesthetic effect exerted by inhibiting and destabilizing potassium voltage gated ion channels.[37,38] Low concentrations of 0.2% are also bacteriostatic and concentrations of 1% are bactericidal. Phenol is administered perineural, producing similar histological changes like alcohol (Wallerian degeneration, axonal demyelination). Perineural small blood vessel occlusion and fibrosis has also been reported.[39] Up to 20 mL phenol 5% can be injected at one time (lethal dose is estimated to be 8.5 g), with most likely side effects being short lasting injection site pain and lightheadedness/dizziness similar to being drunk, long lasting deaferentation/dysesthetic pain, and excessive motor weakness. Because phenol has immediate onset of action, it is possible to titrate the dose during one procedure. Nerve stimulation, fluoroscopy, CT guidance should be employed to minimize the occurrence of side effects or more serious complications resulting from direct injection into adjacent structures (deep vein thrombosis, infarction, ischemia, tissue necrosis). Phenol overdose can cause tremor, seizures, CNS depression and cardiovascular collapse.

Local Anesthetics

Lidocaine and Bupivacaine are amide-type local anesthetic that induce reversible nerve conduction blockade by increasing the depolarization threshold through interacting with D4–S6 portion of the alfa subunit of the voltage gated sodium channel. The blockade affects nerve fibers in both sensory and motor (afferent/efferent) loops. Clinically, after administration, decrease in pain, temperature, touch, and proprioception occur before decrease in skeletal muscle tone. Delivery is achieved by topical administration or injecting it subcutaneous, intradermal, or submucosal, around the nerve trunks or ganglia supplying the area of interest. The role of anesthetics in spasticity management is to answer clinical questions like: what is the role played by spasticity in a joint contracture/range of motion deficit; which muscles are contributing to pathologic posturing; how strong are the opposing/antagonistic muscles; would a block improve function. Anesthetic blocks are used thus as diagnostic tools rather than therapeutic ones. With the most common delivery used in focal spasticity management (perineural infiltration), the onset of action is within minutes and duration of action varies between one and several hours according to the agent used (lidocaine can last for one to three hours, while bupivacaine can last up to 8–10 hours). Bupivacaine is about 10 times more lipid soluble than lidocaine, making it more potent. Lidocaine is 64% protein bound and bupivacaine 95%, making the latter last longer. Lidocaine half life is two hours and bupivacaine half life is 2.7 hours. Both are extensively metabolized in the liver primarily mediated by CYP1A and CYP3A subfamilies and are excreted by the kidneys, with less than 10% in unchanged form. Common dose used for peri-neural infiltration is 1–5 mL of Lidocaine 1% or Bupivacaine 0.25%–0.75%, depending on the size of the targeted nerve. Maximum recommended dose for intramuscular/perineural injection is 0.18 mLrkg. Side effects are related mostly to the type of drug delivery, injection, and consist of pain and erythema at the injection site. Nerve damage by direct trauma from the needle or prolonged exposure to a high concentration of local anesthetic is also possible. Direct injection into the muscle of highly concentrated anesthetic solution can cause muscle necrosis. Systemic toxicity can occur with intravascular injection and manifests progressively with peri-oral tingling, metallic taste, slurred speech, dizziness, diplopia, tinnitus, confusion, seizures, bradycardia, heart block, cardiac arrhythmias, and death.

Botulinum Toxin

Botulinum toxins are neurotoxins produced by Clostridium botulinum and they inhibit release of acetylcholine at the neuromuscular junction, thus inducing weakness/paralysis. There are seven type specific, distinct neurotoxins, A through G, that share a common structure consisting of a heavy chain and a light chain linked by a disulfide bond. Each toxin type is presumed to interfere with a different fusion protein responsible for docking and releasing the achetylcholine vesicle at the presynaptic membrane level. Only botulinum toxin type A, B, C, and F have been studied in clinical circumstances and only botulinum toxin type A and B are FDA approved for clinical use in United States.

Botulinum toxin type A (Botox, Dysport) is an intramuscular toxin produced from fermentation of *Clostridium botulinum* type A. It is one of seven toxic serotypes of botulinum (A through G) that have been purified. Botulinum toxin type A acts by blocking neuromuscular conduction through presynaptic inhibition of acetylcholine release. Partial chemical denervation of the muscle occurs as the neurotoxin cleaves SNAP-25 fusion protein, which is necessary for successful docking and release of acetylcholine from the vesicles situated within nerve endings. Botulinum toxin type A is administered by local intramuscular injection. Absorption is minimal and measurable concentrations of the toxin are not expected to be present in the peripheral blood following intramuscular (IM) injection at the recommended doses. Anecdotal reports of dysphagia occurrence after upper extremity injection points to some systemic effect; subclinical systemic effects have been shown by single-fiber electromyography after IM doses of botulinum toxin. The onset and duration of action depend on the clinical use of the drug. In treating spasticity associated with SCI, the onset of action is usually two to six days; peak of action is reported to occur at four to six weeks and the effect is usually gone by three months post injection. There are suggested doses for specific indications and site of injection. In clinical practice, repeated injections at the same site may increase the duration of action of subsequent doses. To prevent development of neutralizing antibodies, it is suggested that injections are repeated no more frequent than every three months. Injection is done with freshly reconstituted toxin solution (reconstitution needs to be done up to four hours prior to injection, utilizing preservative free normal saline). Rough handling during reconstitution is to be avoided as it can inactivate the biologic effect. The most commonly reported drug related side effects are pain at the injection site and focal weakness. Dysphagia, dyspnea, flu-like symptoms, nausea/vomiting have also been reported. The human LD50 (minimal dose that killed 50% of injected Swiss-Webster mice) has been estimated to be approximately 2,800 units. There have been rare reports of adverse reactions involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes, although the relationship to the toxin has not been established.

Botulinum toxin type B (Myobloc, Neurobloc) is produced from fermentation of *Clostridium botulinum* type B. It is also a neurotoxin that acts at presynaptic junction by heavy chain mediated neurospecific binding of the toxin with internalization of the toxin by receptor mediated endocytosis and adenosine triphosphate (ATP) and pH dependent translocation of the light chain to the neuronal cytosol where it acts as a zinc-dependent endoprotease, cleaving Vesicle Associated Memebrane Protein (VAMP/synaptobrevin). Vesicle Associated Memebrane Protein, like SNAP-25, is essential for docking and fusion of the synaptic vesicle to the presynaptic membrane. Botulinum toxin type B is administered by intramuscular injection. The recommended initial dose of botulinum toxin B for patients with history of tolerating botulinum toxin A is 2500–5000 units. For patients that never had botulinum toxin injections, the recommended starting dose is lower. Maximum effect occurs at four to six weeks and lasts for 12–16 weeks. Injection is done with already reconstituted neurotoxin; the solution contains human serum albumin, theoretically carrying the risk of viral disease transmission. The solution is much more stable than Botox, lasting up to 21 months under refrigeration. Once open, the solution needs to be used within a four hour window, as it does not contain a preservative. Most commonly reported drug related side effects are dysphagia, dyspepsia, injection site pain, and xerostomia. A recent report describes severe dysphagia following Myobloc injection to legs and paraspinal muscles in a 29 year old with spastic diplegic cerebral palsy.[40] The human LD50 for botulinum toxin B is estimated to be up to 20% higher than for botulinum toxin A. Toxicity manifests as severe muscle weakness and paralysis. Antitoxin is available from CDC, although shortage is reported.[41]

Promoting regeneration and recovery

In addition to treatment of spasticity associated with SCI, there is great interest in promoting regeneration and recovery of function using cell based therapies and other modalities. Cellular targets for these interventions are shown in Figure **9–3**. To date, nearly a dozen prospective clinical trials have been completed,[10] many of which focus on limiting secondary injury. Whereas researchers used to believe that spontaneous regeneration was limited in magnitude and duration, many now believe that continuous plasticity offers the potential for optimizing regeneration even long after the injury.[1,42] One approach used in our center focuses on the concept of activity-dependent neuronal plasticity to promote recovery of function. This concept arose from developmental neuroscience and clinical studies of outliers, such as the man shown in Figure **9–1**.[1,9,43–44] After spinal cord trauma, patterned neural activity is dramatically reduced below the injury level,[45] because efferent signals from the brain cannot descend through the injured site and, perhaps more importantly, the spinal cord no longer receives patterned sensory feedback from the limbs. Because the cellular events that occur during development are the same as those that would promote regeneration, it is likely that patterned neural activity is equally important for optimizing cellular regeneration.

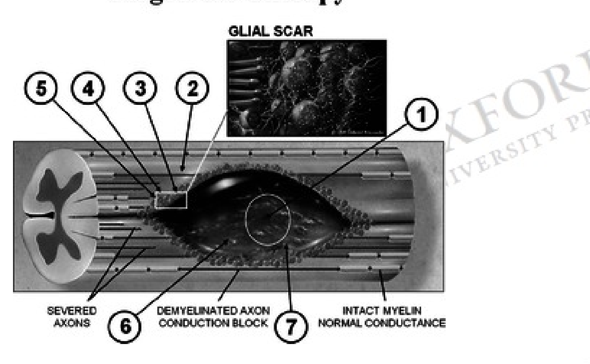




Figure 9–3.
1. Prevent cyst expansion; 2. Re-myelination; 3. Prevent scar; 4. Re-direct axons; 5. Promote axonal regenerations; 6. Replace cells; 7. Create bridges.

Our group recently examined the hypothesis that inducing patterned neural activity in the spinal cord might harness the restorative potential of endogenous stem cells. This activity-based restoration hypothesis is best tested in the laboratory, where activity can be artificially enhanced after experimental spinal cord trauma using functional electrical stimulation (FES) or pharmacological agents or reduced using clinically relevant pharmacological agents such as Baclofen. Our recent data from a rat model of SCI support the hypothesis that optimized patterned neural activity is important for spontaneous regeneration. We demonstrated that FES enhances regeneration while concomitant treatment with Baclofen reduces regeneration and recovery of function. For example, after we induced chronic SCI by complete suction ablation of the mid thoracic cord in a rodent model, we were able to produce a gait-like activity in the animals' hind limbs by linking an FES device to the peroneal nerves. This activity enhanced neural cell proliferation in the sub-injury levels of the spinal cord that are predicted to receive the FES-induced patterned neural activity. A 60%–70% enhancement of new cell birth, which translated into long-term cell survival, occurred in the lumbar levels of the cord, whereas rates of cell birth and cell survival remained unchanged above the injury level.[9] Moreover, when we transplanted embryonic stem (ES) cell-derived tripotential precursors into the SCI model described previously, we found that FES selectively induced the differentiation of neurons rather than the usual glia (unpublished observations). Thus, as well as increasing neural cell birth and survival, FES also affects cell fate by encouraging the production of neurons.

When we used Baclofen in our rat model of SCI, we observed a profound reduction in the number of progenitor cells because the drug decreased cell birth and subsequent cell survival. It also reduced the differentiation of neural cells. Thus, this common antispasmodic agent, which is frequently needed in progressively higher doses, dramatically impaired recovery of gait as well as cellular regeneration. Early data from other fields predicted these results. In the 1980s, Taub and colleagues demonstrated that single doses of Valium can impair recovery from stroke in rodent models of forepaw function.[46] Therefore, it is important to rethink postacute and chronic treatments for complications of SCI because such treatments may have the unforeseen consequence of impairing regeneration and functional recovery.

Conclusion

Spasticity is a challenging clinical problem, but one with important and rewarding functional benefits to individuals with CNS injury, particularly disorders of SCI. The framework for treatment is based in the understanding of anatomy, physiology and pharmacology. Important systemic changes in patients with spinal cord injuries influence their response to drugs used to treat spasticity. Together with clinical experience, the clinician is armed adequately to optimize treatment to maximize function and quality of life for individuals with SCI. However it is important to understand the excessive treatment may actually impair recovery in certain cases because of reduced neuronal activity. Research in this arena is beginning to transform our understanding of physiology and function of the spinal cord and CNS, the pathophysiological consequences of injury, the capacity for spontaneous regeneration and factors important to optimize regeneration and recovery of function. This shifting understanding coupled with rapid advancement of pharmacological tools requires today's neurologist to reevaluate previous treatment goals and guidelines, particularly in this new era of regeneration.

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Neuromuscular Disease

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Neuromuscular disorders encompass a broad spectrum of disease processes and anatomical dysfunction. In the past, pharmacological therapies of neuromuscular diseases have focused on providing symptomatic relief. In the last several decades, neuromuscular pharmacology has broadened its aims to include both symptom-altering agents and disease modifiers. The labors of neuromuscular research have provided clinicians with multiple classifications of pharmacologic therapy to address the individual needs of the neuromuscular patient.

Neuromuscular disease can be divided into anatomical subgroups. These groups include diseases of the: muscle, neuromuscular junction, peripheral nerve, plexus, nerve root, and anterior horn cell. These subgroups represent a myriad of neuromuscular diseases. The goal of this chapter is not to provide a detailed description of each individual neuromuscular disease, but rather to concentrate on the classification of pharmacologic therapies available to each group. This chapter will focus on representative diseases that utilize various classifications of therapy. In addition, specific mechanism of action and justification for use of each medication will be provided based on both historic and contemporary randomized clinical trials.

The classification of current neuromuscular drug therapies

There are 12 main classifications of drug therapy for patients with neuromuscular disease (Table 10–1). These classifications are grouped primarily by their mechanisms of action and include:

1. Immune modulating medications
2. Neuromuscular junction agents
3. Glutamate inhibiting agents
4. Vitamin supplements
5. Enzymatic replacements
6. Preventive vaccines
7. Toxin reducing agents
8. Channelopathy altering agents
9. Antimicrobial agents
10. Antimyotonic medications
11. Duchenne muscular dystrophy altering agents



12. Diet supplements

Table 10–1 Classes of Neuromuscular Therapies

Representative Disease	Medication	Indication	Notes
			IMMUNE MODULATING MEDICATIONS
Myasthenia Gravis	Corticosteroids	First-line	Monitor for hypertension, hyperglycemia, cataracts and weight gain. Consider prophylaxis medications to limit osteoporosis and gastrointestinal reflux.
	Plasma Exchange	First-line	Effective abortive and prophylactic agent. Disadvantages include high cost, short lived effects, and invasiveness. Contraindications include coagulopathy, thrombocytopenia, septicemia, or cardiovascular instability.
	IVIG	First-line	Effective abortive therapy. Side effects may include rash, aseptic meningitis, cerebral infarction, headache, hemolytic anemia, transient lymphopenia and renal failure.
	Azathioprine	Second-line	Delayed beneficial effects. May cause bone marrow suppression, hepatic toxicity, pancreatitis, teratogenicity, oncogenicity and an increased rate of infection.
	Mycophenolate Mofetil	Second-line	May cause bone marrow suppression, infection, neoplasia, or teratogenicity.
	Cyclosporine	Third-line	May cause renal toxicity, hypertension, electrolyte imbalance, intestinal upset, oncogenicity, or infection.
	Cyclophosphamide	Third-line	Useful in refractory cases. May cause bone marrow toxicity, hemorrhagic cystitis, teratogenicity, sterilization, infection, and dose related malignancies. Frequent monitoring of blood count and urinalysis is needed.
	Tacrolimus	Third-line	Side effects similar to Cyclosporine.
Dermatomyositis	Corticosteroids	First-line	Oral dosages may be given for chronic care. IV dosages are often used for abortive therapy during disease flares.
	IVIG	Second-line	Can be used in combination with other immune modulating medications
	Methotrexate	Second-line	Effective add-on therapy. Delayed treatment effects. May cause pulmonary fibrosis, teratogenicity, oncogenicity, increased risk of infection, bone marrow suppression, or renal/liver toxicity.
	Azathioprine	Second-line	Effective add-on therapy. Less effective if antisynthetase autoantibodies are present. There is a six month delay for treatment effects.
Chronic Inflammatory Demyelinating Polyneuropathy	Corticosteroids	First-line	Treatment effects often take several weeks.
	IVIG	First-line	Treatment effects can be seen in a week. The maximal benefit from IVIG often takes six weeks.
	Plasma Exchange	First-line	Short lived effects are common (2–8 weeks).
Multifocal Motor Neuropathy	IVIG	First-line	Long term benefits in 60% of patients
	Cyclophosphamide	Second-line	Effective in 70% of patients; however, serious dose related toxicities exist.
Guillain-Barre Syndrome	IVIG	First-line	Shown to decrease disability at four weeks. Treatment should be started early if no contraindications.
	Plasma Exchange	First-line	Most effective when given within seven days of symptom onset.
			NEUROMUSCULAR JUNCTION AGENTS
Myasthenia Gravis	Acetylcholinesterase Inhibitors	Symptom Relief	Overdose may produce a cholinergic crisis: weakness, diarrhea, cramps, lacrimal discharge, salivation, miosis, nausea, abdominal pain.
Lambert-Eaton Myasthenia Syndrome	3–4 Diaminopyridine	Symptom Relief	Improves strength and autonomic symptoms. May cause paresthesias and seizures. Available only for compasionate use.
	Acetylcholinesterase	Symptom	Pyridostigmine bromide improves dry mouth, but does not clearly effect strength. Patients should

	Inhibitors	Relief	be monitored for signs of cholinergic crisis.
	Guanidine	Symptom Relief	Add on therapy to the acetylcholinesterase inhibitors. 50% develop gastrointestinal side effects and some may experience bone marrow depression, liver dysfunction, renal insufficiency, tremor and ataxia.
GLUTAMATE INHIBITING AGENTS			
Amyotrophic Lateral Sclerosis	Riluzole	First-line	Extends life by several months. May cause nausea, asthenia, and elevated liver enzymes.
	Dextromethorphan Hydrobromide and Quinidine Sulfate	Experimental	Combination therapy that may reduce pseudobulbar effects in ALS.
ENZYMATIC REPLACEMENTS			
Fabry's Disease	Alpha-galactosidase A	First-line	IV preparation found to reduce pain, decrease mesangial widening, increase kidney function, and improve cardiac conduction. 48% of patients develop rigors on this medication.
Acid Maltase Deficiency	Human Precursor Alpha-Glucosidase	First-line	IV preparation may maintain left ventricular mass, and muscle strength. Bare side effects may include heart failure, respiratory failure, allergic shock, pneumonia, infections and fever.
TOXIN REDUCING AGENTS			
Plumbism	Chelating agents	First-line	Calcium disodium versenate (CaEDTA), British anti-lewisite (BAL) in oil, cuprimine, chemet. A combination of CaEDTA and BAL may be used for more severe intoxications.
Botulism	Botulism Immune Globulin (BIG)	Becommended	Human and equine forms available. Adults should be tested for hypersensitivity before given the equine form. Use may reduce the length of a patient's hospital stay. Side effects may include hypertension, dermatitis, or atelectasis.
	Trivalent Antitoxin	Becommended	Minimizes the progression of nerve damage but does not reverse paralysis. May cause a hypersensitivity reaction.
Thallium Toxicity	Berlin Blue	First-line	Beduces the elimination half-life of thallium from 8 to 3 days.
CHANNELOPATHY ALTERING AGENTS			
Hypokalemic Periodic Paralysis	Potassium	First-line	Can be given for daily maintenance. Oral dosages are absorbed quicker than pill forms. Close cardiac and electrolyte monitoring is requiring if IV doses are given.
	Carbonic Anhydrase Inhibitors	First-line	Improves weakness. Serial blood counts and liver enzyme profiles should be performed. Dichlorphenamide is a more potent agent than acetazolamide.
	Potassium Sparing Diuretics	Second-line	Triamterene or spironolactone. May be used as daily therapy. Potassium levels must be monitored closely when used in conjuction with potassium supplements.
Hyperkalemic Periodic Paralysis	Thiazide	First-line	Diuretic. Side effects may include: allergic reactions, weigh loss, nausea, confusion, thrombocytopenia and hypotension.
	Carbonic Anhydrase Inhibitors	First-line	Reduces the severity and frequency of attacks. Exact mechanism of action is unknown.
	Glucose and Insulin	Severe Hyperkalemia	Under close monitoring these agents can be used to reduce potassium levels quickly and safely.
ANTIMYOTON MEDICATIONS			
Myotonic Dystrophy Type-1	Mexiletine	First-line	A class IB antiarrhythmic that is safe and effective in reducing mytonia. Blood counts, liver function, and electrocardiograms should be followed.
	Tricyclic Antidepressants	Second-line	Imipramine and Clomipramine. May reduce grip myotonia. Side effects may include sedation, hypotension, arrhythmias, dry mouth, constipation, reduced sweating, weight gain, and sexual dysfunction.
	Taurine	Second-line	Reduces perceived myotonia and EMC relaxation times. May cause a generalized amino aciduria.
DIET SUPPLEMENTS			
Mitochondrial Disorders	Co-Enzyme Q10	Proposed Therapy	Limited studies demonstrate mild improvement in strength and clinical status. Naturally produced by the body.

	Creatine	Proposed Therapy	Limited studies have reported increased strength. Serious side effects at high doses include renal failure, and rhabdomyolysis.
	Sodium Dichloroacetate	Proposed Therapy	May reduce lactate, pyruvate and alanine after exercise. Reported side effects include fatigue, shortness of breath, gastrointestinal distress and tremor.
McArdle's Disease	Creatine	First-line	Low dosages may improve symptoms and increase tolerance of workload.
	Sucrose	Proposed Therapy	Given before exertion may reduce perceived exertion and maximal heart rate.

Some patients with neuromuscular diseases such as myasthenia gravis, may benefit from simultaneous treatment from several of the these therapeutic classifications. Conversely, some neuromuscular diseases have yet to show any substantial benefit from any of these classes of therapy. In neuromuscular diseases refractory to the therapies, supportive, nonpharmacologic care is provided in the form of orthotic braces, physical and occupation therapy, assisted mobility devices, social services, and general counseling.

Following is specific information on the different classifications of neuromuscular drug therapies and representative diseases that utilize these therapies.

Immune modulating medications

Immune modulation is one the hallmarks of neuromuscular disease drug therapy. This classification of therapy is used broadly in diseases that either have an autoimmune component, or a prominent inflammatory response. The beneficial actions of immunomodulating agents may occur from their effects on B-cell mediated humoral immunity or T-cell mediated immunity. These agents are often initially selected based on what is known about individual disease processes, and the hypothesized mechanism of action of individual medications; however, standard of care is ultimately determined through observed clinical response in randomized trials.

Representative Diseases That Use Immune Modulating Medications

Myasthenia gravis (mg)

Myasthenia gravis is a neuromuscular disease in which circulating antibodies against the acetylcholine receptor bind to the postsynaptic nicotinic acetylcholine receptors. This binding process limits the availability of receptors for acetylcholine and may directly damage postsynaptic membranes through complement activation.[1] The reduction in acetylcholine receptor availability reduces the opportunity for sufficient stimulation of end plate potentials to exceed threshold for muscle fiber contraction following repetitive nerve stimuli and manifests clinically primarily through fatigable muscle weakness.

Autoantibodies made against the acetylcholine receptor in MG appear to result from a T-cell-dependant process.[2] Antibodies may block binding by acetylcholine, modulate receptor characteristics, and increase complement mediated lysis of receptors. Such lysis leads to widening and simplification of the postsynaptic folds and may cause loss of voltage-gated sodium channels. Pharmacologic strategies include the use of acetylcholinesterase inhibitors (see Neuromuscular Junction Agents further on in this chapter). Acetylcholinesterase inhibitors prolong the availability of acetylcholine to find a binding site, which produces transient symptomatic benefit and immune modification. A major nonpharmacologic treatment consists of a therapeutic thymectomy secondary to the role that the thymus has in mediating an enhanced responsiveness of lymphocytes to foreign antigens.[3,2] The degree of therapeutic benefit of thymectomy remains a matter of varying opinion and is currently being evaluated in a multicenter randomized clinical trial.

The most common clinical manifestations of MG include fatigable, intermittent weakness that typically causes bulbar symptoms, such as dysarthria or dysphagia, and extraocular weakness as demonstrated by diplopia and/or ptosis. A life threatening crises may occur in MG causing severe, often generalized, weakness and respiratory compromise. Such events require close monitoring and at times endotracheal intubation until symptoms abate.

The diagnosis of MG is based on clinical features, the presence of positive acetylcholine receptor antibody tests (sensitivity of 90%), and characteristic electrodiagnostic features.[2] Electrodiagnostic features may demonstrate a decremental response in the amplitude of compound motor action potentials (CMAPs) with 2–3 Hz stimulation, and the presence of increased jitter through single-fiber testing. An elevated level of antistriational antibodies may suggest the presence of a coexisting thymoma. Tensilon testing in the opinion of the authors is not a recommended diagnostic tool due to its potential side effects and lack of both sensitivity and specificity.

The autoimmune etiology of MG has led many to evaluate varying immune modification agents. Corticosteroids were the first to be used with promising effects. However, other modifying agents have more recently gained popularity due to the long-term undesirable side effects of corticosteroids, the modifying agents' corticosteroid sparing effects, and lastly their ability to reduce symptoms to an extent comparable to that observed with corticosteroid therapy alone.

The immunosuppressant treatment of mg

The use of oral corticosteroids in MG was initially based on observational reports, theoretical benefit, and expert opinion. More recently, randomized trials have demonstrated the shortterm benefits of corticosteroids compared to placebo.[4] Through metaanalysis of past studies it has been shown that varied dosing regiments of prednisone can cause marked clinical improvement in 63.4% to 80.2% of patients, with complete remission occurring in 27.6% to 41.6% of all patients.[4] Unfortunately, 52% of the myasthenia patients studied on corticosteroid therapy developed one of the following side effects: osteoporosis, diabetes mellitus, infection, gastric ulcer, or glaucoma.[4]

Intravenous steroid preparations are also used in myasthenia patients. Compared to placebo, pulse IV methylprednisolone can improve muscle function in patients with moderate symptoms with a mean duration of improvement lasting eight weeks after therapy.[5] The benefit of intravenous preparations over oral preparations is less clear. In one study of patients with juvenile MG, oral prednisone at 1 mg/kg/day with a tapering schedule did not demonstrate a substantial difference in efficacy compared to a high dose intravenous regimen of methylprednisolone over 14 weeks; however, the patients receiving intravenous therapy reached sustained and maximal improvement more quickly.[4,6]

Due to its longevity of use in MG, corticosteroids are held as the gold standard when evaluating other immune modulating medications. To this end, new agents are often compared to corticosteroids (instead of placebo), or studied as an add-on agent to preexisting corticosteroid use. Despite the commonly held belief that corticosteroids relieve myasthenia symptoms, debate still exists regarding the optimal starting dosages, tapering schedules, titrating schedules, and length of corticosteroid use for symptomatic myasthenia patients. The following five alternatives to corticosteroids have all shown promise in the treatment of acquired autoimmune MG. Specific drug profiles are provided at the end of the section.

Azathioprine has emerged as a beneficial immune modulating agent for myasthenia patients. Studies comparing azathioprine to prednisone showed similar improvements in muscular score, functional grade, and time to remission, and patients taking azathioprine experienced a lower incidence of side effects.[7] When used in conjunction with prednisolone, azathioprine at 2.5 mg/kg/day is associated with fewer treatment failures, longer remissions, and reduced maintenance doses of prednisolone.[8,9] Numerous other studies have suggested the benefit of azathioprine as maintenance therapy in MG, but have not been randomized or prospective.[8]

Mycophenolate mofetil is another immune modulating drug showing beneficial effects in myasthenia. Three open label trials have demonstrated tolerability, improved functional status, and reduced steroid requirement. In one open label trial, eight of twelve patients showed improvement based on assessments of strength, quantitative MG score, and reduction in corticosteroid therapy after six months of mycophenolate mofetil (1 gram twice daily) and no patients developed any major side effects.[10] In a 12 month trial of mycophenolate mofetil, 22 of 32 patients showed either an improvement in functional status or a reduction in corticosteroid use.[11] Of those that showed improvement, their mean time to benefit was five months.[11] A retrospective study analyzing data from 85 patients with MG treated with mycophenolate mofetil showed benefit in 73% of patients with only 6% of patients having to discontinue treatment due to side effects.[12] Further studies evaluating the use of mycophenolate mofetil in MG patients are currently underway.

The usefulness of immunosuppressive therapy with cyclosporine in MG is less clear. In one placebo-controlled double-blind randomized trial of 20 patients, individuals receiving 6 mg/ kg/day of cyclosporine had greater improvement in strength and greater reductions in acetylcholine receptor antibody titers compared to those receiving placebo. Unfortunately, a direct comparison against corticosteroid therapy was not performed, and 3 of the 20 patients receiving cyclosporine developed a reversible nephrotoxicity secondary to the cyclosporine.[8,13]

The antimetabolite/immunosuppressive drug, cyclophosphamide, is not a first line treatment for MG, but it has been effective in refractory cases. In 23 patients with either poor disease control or steroid-related side effects, muscle strength and dependency on methylprednisolone use were improved with pulse intravenous cyclophosphamide compared to placebo.[14] Unfortunately, the potential serious side effects of cyclophosphamide limit its potential for widespread use in MG.

Tacrolimus, an immunosuppresant commonly used in organ transplantation, has also been used for MG. In a 16 week trial using low dosage therapy 37% of patients with generalized myasthenia had clinical improvement and there was a reduction in acetylcholine receptor antibody titers.[8,15] Like cyclosporine and cyclophosphamide, the potential side effects prevent tacrolimus from becoming a first-line therapy.

Immunomodulating agents in the treatment of myasthenia crisis

In addition to the chronic, fluctuating symptoms that trouble some patients, MG may quickly progress into a myasthenia crisis. Myasthenia crisis is a severe and potentially life threatening bulbar and respiratory dysfunction that may develop rapidly in both treated and untreated patients. Initiation of most immunosuppressive therapies is not effective as acute treatment for crisis due to the delayed time required to achieve beneficial effects. Fortunately, two therapies currently exist (plasma exchange and intravenous immunoglobulin infusion, IVIG) that can improve symptoms and provide benefit to patients in myasthenia crisis.

Plasma exchange is widely utilized in myasthenia crisis. Multiple case series demonstrate its benefit in crisis.[16] In one series published in 2000, 79 of 94 patients received treatment with plasma exchange for poor clinical control, as a presurgical preparation, or for crisis. In all groups there was an improvement in muscle score.[17,18] In 1986, an appointed scientific panel at a National Institute of Health (NIH) conference approved the use of plasma exchange and discouraged (on ethical grounds) a controlled trial for its use in myasthenia crisis based on the clear benefits shown in prior case studies.[16,17] Given this recommendation, it is unlikely that a placebo-controlled randomized trial will ever be carried out to evaluate the efficacy of plasma exchange in myasthenia crisis.

While the short-term benefits of plasma exchange are apparent, meta-analysis has yet to definitively validate its long term benefits.[16] Clinicians typically expect that patients will have at least a two to three week improvement from a course of five standard plasma exchange treatments. Further research is needed to determine the optimal dosing, scheduling and conjunctive use of plasma exchange with other therapies.

The benefits of IVIG in patients with MG is comparable to those obtained through plasma exchange use. A metaanalysis of five randomized controlled trials of IVIG in MG has shown no difference in efficacy between IVIG and plasma exchange in treating exacerbations of MG and the side effects of IVIG were more self-limiting and less severe.[7] An open-label study of 10 myasthenia patients who had acute deterioration and failed response to high-dose corticosteroids, cyclosporine, and azathioprine showed that IVIG given in dosages of 400 mg/ kg/day for five days followed by maintenance infusions every six weeks decreased fatigue and increased strength and respiratory function with no observed side effects.[19] Intravenous immunoglobulin is an useful alternative to plasma exchange in acute exacerbations of MG, in preparation for thymectomy, or as an adjunctive therapy.[7,20]

The usefulness of IVIG as a chronic maintenance therapy for MG is less clear. Outside of acute exacerbations, the efficacy of IVIG in moderate to severe MG has been shown to provide similar benefit compared to plasma exchange four weeks after treatment, although plasma exchange was superior in improving the quantitative MG score compared to IVIG at one week post therapy.[21] In addition, metaanalysis has not shown conclusive evidence for IVIG use as a steroid reducing agent or as an isolated agent for severe to moderate MG.[7] Conversely, individual case series have shown promising reductions of disease severity and reduction in prednisone and azathioprine use in patients receiving treatments of IVIG consisting of a total dose of 2g/kg over five days followed by 0.4g/kg every six weeks.[7] Further studies are necessary to validate the benefit of chronic maintenance IVIG therapy in MG.

Inflammatory myopathies

There are multiple pathomechanisms that may induce an inflammatory myopathy, and they cause a variety of disorders. These disorders include but are not limited to: dermatomyositis, polymyositis, inclusion body myositis, parasitic illness, viral illness, systemic vasculitis, sarcoidosis, polymyalgia rheumatica, rheumatoid arthritis, mixed connective tissue disease, lupus, Sjogren's syndrome and scleroderma.[22]

Of these diseases, dermatomyositis, polymyositis, and inclusion body myositis can be differentiated through their tissue pathology, clinical features, association with malignancy, and response to treatment. Dermatomyositis and polymyositis will be discussed given their favorable clinical response to immunomodulating medications. Inclusion body myositis, while producing both an inflammatory state and elevated creatine kinase (CK) levels, has not been found to have a robust response to any of the immunotherapeutic agents.[23]

Dermatomyositis (dm)

Dermatomyositis affects both the young and old with more women than men acquiring the disease.[24] The characteristic clinical features of DM are muscle weakness and skin rash. The skin manifestations include a blanching purple butterfly rash over the cheeks and eyelids, a V-shaped rash below the neck, and a diffuse body rash.[25] Patients may also develop indurations at their extensor surfaces (sparing the phalanges), looped, dilated, and hemorrhaged capillaries in their nail-bed skin, cracked, rough skin of their lateral palms (mechanic's sign), a violaceous scaly eruption of their knuckles (Gottron's sign), or soft-tissue calcifications.[25,24] The weakness of DM is typically proximal and may be painless or associated with cramping, aching, or unspecified pain.[25] In children, flexion contractures can occur, for example, at the ankle causing a tip-toed gait.[24] Adults with DM have an increased frequency of malignancy, usually carcinoma, which is proportional to the age of disease onset.[25]

Dermatomyositis is a humorally mediated microangiopathy. There is complement c5b-9 membrane attack complex deposition in the capillaries of affected tissues and a predominance of B and Cd4 helper cells in affected blood vessels.[25] With pronounced disease in a given muscle, multiple capillaries become occluded and produce micro-infarctions in fibers especially in the perifasicular region leading to the frequently observed finding on biopsy of perifasicular atrophy.

The diagnosis of DM is based on clinical features, CK elevation, hyperirritable myopathic electromyography (EMG) results, and the characteristic muscle biopsy features of perivascular inflammation, endothelial hyperplasia, perifasicular atrophy, and major histocompatibility complex (MHC) class 1 antibodies in the perifasicular regions.[25] Transfer RNA sythetase and Jo-1 antibody against histidyl tRNA synthetase are present in more than 20% of patients with DM and is a relatively specific finding. Anti Mi-2 antibodies are also relatively specific to DM, but have a poor sensitivity for the disease.[25]

Prognosis in DM is variable. Dermatomyositis typically develops over weeks to months and may relapse and remit or occur as a monophasic illness with spontaneous recovery.[25] Necrosis of muscle fibers that is nonreversible may occur with longstanding disease.[24] In a study of 69 patients with either DM or polymyositis, a survival rate was found to be 82.6% at one year, 73.9% at the second year, 66.7% at the fifth year, and 55.4% by the ninth year with the most significant prognostic factors being the presence of old age, dysphonia, pulmonary interstitial fibrosis, and the absence of myalgia, dysphagia, and anorexia.[26] Unfortunately, much of the information in this report came from patients who had their diagnosis of DM and polymyositis based on less rigorous histopathological criteria than are now applied to investigate these disorders. More studies are necessary using more recent diagnostic criteria to provide a more accurate assessment of long-term prognosis.

Polymyositis (pm)

Polymyositis is an inflammatory myopathy that occurs mainly in patients beyond their second decade and is considered a diagnosis of exclusion.[24] This limitation in precise diagnosis poses a problem in rigorous analysis of published studies of PM and in its response to treatment. Polymyositis is probably not as common as previously believed in adults, and it occurs infrequently in the pediatric population.[25] Unlike DM, there is no associated rash, but PM is clearly not “DM without a rash”. Polymyositis is mediated by cytotoxic T-cells. CD8 T-cells mediate antigen-directed and MHC-I restricted cytoxicity with a predominance of T (T8 greater than T4) lymphocytes.[27] Many past studies have not used careful histopathological staining and classification of lymphocytic infiltrates to identify patients with PM. In these studies it is important to realize that the patients are likely to have a mixture of different forms of inflammatory myopathy with different underlying pathomechanisms and different responses to standard treatment regimens for PM. Occasionally, PM is linked with other connective tissue diseases.[28] Such cases are known as “overlap syndromes.”

The weakness of PM is usually generalized, progressive, occasionally fluctuating, proximal greater than distal and not infrequently associated with malaise, fever, dysphagia, esophageal motility problems, cardiac conduction defects, cardiomyopathy, anorexia, and anti-Jo-1 antibody associated interstitial fibrosis of the lung.[25,27] Like DM, PM affects more women than men and may occur with a concordant malignancy. The weakness in PM takes months to years to develop and progresses more slowly than that in DM.[25,27]

Diagnosis of PM is based on the absence of a secondary cause of inflammatory myopathy in the context of muscle weakness, elevated CK levels, a hyperirritable myopathic EMG, Anti Jo-1 antibodies (in 20% of patients), and a characteristic muscle biopsy. Muscle biopsy findings show scattered fiber necrosis with inflammation around and invading non-necrotic muscle fibers in the absence of perifascicular atrophy.[25] Necrotic muscle fibers tend to be scattered and do not necessarily correspond to the areas of inflammation.[24] Polymyositis may also have endomysial inflammatory infiltrates consisting of CD8 T-cells invading non-necrotic muscle fibers that express major histocompatibility complex class I molecules on the sarcolemma.[28]

The treatment of dm and pm

The treatment of DM and PM is based on immunomodulation. Corticosteroid use is the first-line therapy for both disorders. In cases of relapse, severe weakness, myocarditis, interstitial lung disease, or if a contraindication to corticosteroid use exists, second-line agents such as methotrexate, azathioprine, and IVIG are utilized.[23]

Corticosteroid use in varied forms is effective in both PM and DM. Three day courses of intravenous solumedrol are often recommended for patients presenting with severe weakness, life threatening myocarditis or lung disease.[23] In one study, three of seven juvenile DM patients had complete resolution of symptoms after intravenous pulse dose solumedrol.[29] Oral prednisone alone provided effective therapy allowing a return to baseline strength in up to 66% of patients with DM.[23] In PM, 80% of patients receive benefit from prednisone and up to 33% return to a normal state within a six month period with use of this medication.[23]

Standard dosages of prednisone for PM and DM are 1.0–1.5 mg/kg per day. An objective improvement in muscle strength is usually seen by the third month of treatment.[24] If benefit is not observed at three months, a tapering of the prednisone and the addition of another agent should be considered. Patients may be switched to an alternative day dosing schedule at two to four weeks if there is no sign of refractory disease, severe clinical impairment, or difficult to control serum glucose levels.[23] When a patient’s strength returns to baseline, a slow taper (5 mg every 2–3 weeks and 2.5 mg every 2–3 weeks after dosages of 20 mg every other day are reached) may be attempted as long as relapse does not occur.[23] Relapses should be based on clinical features and not solely on serum level of creatine kinase. If strength declines, prednisone dosages can be increased or a second agent added.

Methotrexate is often used as an initial, or add-on therapy in PM and DM, especially in children and in patients with the troublesome skin manifestations of DM. Compared to azathioprine, its action is quicker and more effective in males or patients with positive antisynthetase autoantibodies.[30] Clinical effects are expected within weeks to months of beginning therapy. In a retrospective study of 22 patients with either PM or DM, add-on methotrexate therapy to preexisting prednisone use provided clinical benefit in 17 (77%) of the patients with the average time to clinical improvement being 13–14 weeks.[31] Methotrexate has also been shown to be more effective then a second course of prednisone in relapsing inflammatory myopathy patients.[30] Dosing regimens of methotrexate vary. One recommended course is 7.5 mg/week divided into three doses separated by 12 hour intervals with dose titrations (based on clinical response) of 2.5 mg every 1–4 weeks to a dose of 20 mg/week.[23] If benefit is not obtained at 20 mg/week, intravenous or intramuscular dosages can be used and titrated to higher dosages.[23]

Azathioprine is also used in inflammatory myopathies. In PM and DM 64% of patients taking azathioprine showed improvement of symptoms; however, only 11% had complete response to therapy.[30] Except in patients with positive antisynthetase autoantibodies, patients receiving azathioprine have had more favorable responses compared to those receiving prednisone.[30] Clinically, the presence of this antisynthetase autoantibody should favor the use of prednisone and/or methotrexate over azathioprine. One limitation of azathioprine in PM and DM is its delayed action. Beneficial therapeutic effects may not occur until after six months of use.[23] This was demonstrated in a trial showing no clinical advantage in PM patients taking azathioprine and prednisone (compared to those taking only prednisone) at the end of a three month trial; although at one year’s time, the patients taking azathioprine had lower levels of disability and required lower prednisone dosages.[32] Dose schedules of azathioprine vary; however, 50 mg/day is a standard adult starting dose with slow titration to 2–3 mg/kg/day over many weeks.

The use of IVIG is an effective treatment for DM. In a prospective double-blind placebocontrolled trial of 15 patients with treatmentresistant DM, monthly IVIG infusions for three months improved strength, neuromuscular symptoms, muscle-fiber diameter, capillary diameter, and decreased the expression of both intercellular adhesion molecule 1 and majorhist ocompatibility-complex class I antigens.[33] Intravenous immune globulin also appears to be effective in PM based on retrospective and uncontrolled studies.[23] Intravenous immune globulin can be used in combination with prednisone, methotrexate, and azathioprine. An initial dose of two grams/kg divided over five days is often utilized with repeat doses given on a monthly basis.

When patients with DM or PM have contraindications to, or are refractory to the previously listed medical therapies, third line treatments may be utilized. These regimens include: cyclophosphamide, chlorambucil, fludarabine, cyclosporine, tacrolimus, mycophenolate mofetil, total body irradiation, lymph-node irradiation, and tumor-necrosis factor-α blockers. These therapies have not been used extensively for PM or DM, but have case reports and limited case series supporting their utility.[23] Further experience with these agents is necessary to elucidate the overall efficacy ofthese treatments in DM and PM.

Chronic inflammatory demyelinating polyneuropathy (cidp)

Chronic inflammatory demyelinating polyneuropathy is an autoimmune neuromuscular disease that occurs secondary to cellular and humoral immune responses mediated by peripheral nerve antigens.[34,35] Autoreactive T-cells recognize autoantigens in the systemic immune compartment then activate macrophages that enhance phagocytic activity, cytokines, tumor necrosis factor (alpha), and the release of toxic mediators.[36] Autoantibodies also activate the complement system while potentially blocking epitopes on ion channels and other proteins that are necessary for normal nerve conduction.[36] Ultimately this inflammatory process leads to nerve demyelination and subsequent muscle weakness and sensory deficits.[34] Occasionally, axonal loss may occur as a result of severe demyelination.[35]

Diagnosis of CIDP is based on clinical features, while electrodiagnostic studies, elevated CSF protein, and occasionally nerve biopsy help validate the diagnosis. Published research diagnostic criteria for CIDP exist with varying levels of specificity and sensitivity.[34] Clinically, CIDP produces a progressive symmetric weakness in both the distal

and proximal upper and lower extremities with markedly reduced or absent tendon reflexes. Often the lower extremities are more severely affected. Paraesthesias and anesthesia in a glove and stocking distribution occur, although pain is rare.[37] While disease symptoms can begin at any age, the peak age of onset is between ages 40 to 60.[37] By definition, a patient with CIDP must have progressive symptoms for over two months. This minimum duration of symptoms provides a criterion to separate CIDP from acute inflammatory demyelinating polyneuropathy (symptoms lasting less than one month) and subacute inflammatory demyelinating neuropathy (symptoms lasting from one to two months). Sixty percent of patients with CIDP have a continuous or stepwise progression of symptoms, whereas one third of patients (with a bias towards the young) undergo a relapsing remitting course.[37]

Although 95% of CIDP patients respond to initial treatment with immunomodulating medications, only 40% remain in remission off of medications.[37] Like DM and PM, multiple therapeutic approaches are available for CIDP. Immunosuppression reduces inflammation, decreases demyelination, and prevents secondary axonal degeneration.[36] First-line treatments include corticosteroids, plasma exchange, and IVIG. However, alternative agents such as etanercept, interferon-beta-1a, cyclosporine A, rituximab, and cyclophosphamide, have emerged with varying results as second-line treatments for nonresponders and patients with contraindications to primary therapies.[34,38,37] Still other agents such as interferon-alpha, mycophenolate mofetil, and azathioprine have been tried in CIDP populations with less promising results.[38–40] Further prospective studies are necessary to validate the efficacy of these secondary agents.

The efficacies of IVIG, plasma exchange and oral prednisone in patients with CIDP range from 70% to 80%, making secondary factors such as cost, side effects, duration of treatment, dependency on regular hospital visits and ease of administration important in determining which agent to first utilize.[41,38]

Prednisone is one of the three main treatments of CIDP. A typical initial dosage is 60 mg (or 1.0–1.5 mg/kg in children) given on alternating days. Tapering regimens vary, and tapering is often not appropriate for months to years, or until stabilization and clinical improvement are definitively noted. Benefit from prednisone usually begins after several weeks with maximal effects typically occurring after 3–6 months.[42] Prednisone is thought to alter the pathophysiological processes of CIDP by altering the expression of interleukin (IL)-1, IL-2, IL-6, and tumor necrosis factor while inhibiting T-cell proliferation and T-cell dependent immunity.[42] In addition, prednisone may improve the CIDP suppressor cell function defect and prevent inflammatory cells from entering peripheral tissues though antiadhesion affects.[42]

Intravenous immunoglobin is also an effective treatment of CIDP. Randomized controlled trials show that intravenous immunoglobulin improves disability from CIDP for at least two to six weeks after use. Intravenous immunoglobin is given at 2 g/kg divided over two to five days with maintenance dosages of 0.4–1.0 g/kg every two to six weeks based on benefit. Improvement of symptoms may occur within seven days; however, maximal benefit typically takes six weeks.[37]

Plasma exchange is another effective treatment for CIDP and the usual protocol involves five exchanges of 250 ml/kg liters over 7–10 days with maintenance exchanges every one to three weeks.[38,42] Without the use of maintenance exchanges or additional immunosuppressive agents, patients may relapse from CIDP within two to eight weeks after cessation of plasma exchange therapy.[42] Debate exists about the ideal maintenance schedule of plasma exchange; however, most agree that this should be determined on an individual basis based on the initial clinical response to treatment.

Newer therapies have not been studied as thoroughly as corticosteroids, plasma exchange, and IVIG, but some show early promise in limited clinical trials. Etanercept has been utilized in demyelinating polyneuropathy patients who have initially failed to respond to primary therapies. Etanercept was shown to be efficacious in 6 out of 10 patients receiving dosages of 25 mg subcutaneously twice a week after four to six months.[38] Interferon-beta-1a has also been studied in CIDP. Interferon-beta-la for six months at a dose of 30 μg once a week produced clinical improvement in 35% of 20 treatment-resistant CIDP patients. However, other studies of interferon-beta-la in CIDP have not duplicated these promising results.[38] In a small study of seven CIDP patients, cyclosporine A improved clinical symptoms after one month based on Rankin scores, Inflammatory Neuropathy Cause and Treatment (INCAT) disability scores, and grip strength measurements.[43] Unfortunately, metaanalysis has found the data to be inconclusive in proving efficacy of this medication in CIDP.[44] Likewise, highdose cyclophosphamide therapy has had positive effects on the quality of life, strength, and functional status of five studied patients with severe refractory CIDP, and Rituximab has benefited selected CIDP patients, though large scale studies have yet to be completed.[45,46]

Even with the hypothesized immunologic pathomechanism of CIDP, some immunomodulating therapies have not had positive effects in CIDP. Early data on Interferon-alpha has yet to show benefit and in a study of 27 CIDP patients, no benefit was found in adding azathioprine to prednisone over prednisone treatment alone.[39,40] For other agents, such as mycophenolate mofetil, select case reports proclaim efficacy while conflicting case series show no benefit.[38]

Multifocal motor neuropathy (mmn)

Like CIDP, MMN is a chronic demyelinating immune polyneuropathy. Unlike CIDP, MMN produces an asymmetric weakness with no sensory symptoms. There is a predisposition of this disorder to effect men, and the majority of the people diagnosed with this disease are under the age of 45.[37] The weakness of MMN often begins at the distal arm with associated electrodiagnostic conduction block while atrophy, cramps, and fasciculations may develop months to years later.[37] Nonspecific IgM binding to GM-1 ganglioside may be detected in 80–90% of MMN patients, with cerebral spinal fluid (CSF) protein often being normal.[47] Multifocal motor neuropathy is an important disease to recognize, as it may mimic early amyotrophic lateral sclerosis and should not be confused with this disease.

Immune modulating therapies are effective in MMN. Intravenous immunoglobin with maintenance therapy shows long term benefit in 60% of MMN patients. Cyclophosphamide is effective in 70% of patients, but can have serious dose-related toxicities.[47] Varying dose regimens of cyclophosphamide exist. Six monthly treatments of intravenous (IV) cyclophosphamide (1 g/M^2), with preceding courses of plasma exchange before each treatment are favored by some authorities.[47] Rituximab and interferon-beta-1a have also shown benefit in case series, yet larger studies are needed to verify benefit.[35]

Corticosteroids and plasma exchange in isolation are ineffective treatments in MMN.[36] The explanation for why these medications have profound beneficial effects in CIDP, and have such limited effects in MMN remain to be discovered.

Lewis-sumner syndrome (multifocal acquired demyelinating sensory and motor polyneuropathy)

Lewis-Sumner syndrome is an asymmetric demyelinating polyneuropathy that presents with both motor and sensory symptoms, and an elevated CSF protein. The average age of onset is in the early to mid-50s with an age range of 18–77 years.[48] Weakness and numbness of the arms usually occurs before the legs are affected; pain is a rare feature of this disorder.[48] This acquired polyneuropathy typically begins in the upper extremity and like MMN may have antibodies to gangliosides. Treatment consists of IVIG, steroids, or cyclophosphamide.[36] The efficacy of steroid use in this disorder ranges from 50% to 75%.[48]

Anti-myelin-associated glycoprotein (mag) demyelinating neuropathy

Anti–myelin-associated glycoprotein demyelinating neuropathy is an insidiously progressive sensory or sensorimotor neuropathy with high levels of MAG that develop over months or longer. The clinical features include ataxia, postural tremor, areflexia, and a profound ascending numbness, vibratory loss, and reduction of proprioception sense.[49,50] Most patients are elderly males though only 10% become wheelchair-bound from the disease.[49] Both nerve biopsy and electrodiagnostic studies show demyelinating features. Although not well understood, the pathomechanism is thought to be secondary to monoclonal protein acting with activated complement to damage peripheral myelinated nerve fibers.[50]

Various immunomodulating treatments have been utilized for this condition. In one study, 24 patients with this disorder received three different therapies: plasma exchange, immune globulin, and cyclophosphamide.[51] These therapies had similar therapeutic outcomes, although most patients failed to have sustained improvement and no clear therapy emerged as superior.[51] Other therapies such as corticosteroids, chlorambucil, INF-alpha-2a, fludarabine, rituximab, or combinations of these drugs have also shown transient beneficial effects.[49]

Given the high percentage (30%) of patients who do not have progression of disease symptoms with anti-MAG demyelinating neuropathy and anti-MAG's predisposition to affect elderly patients, the transient benefits of these medications should be carefully weighed against their toxicity before implementing their use.[49]

Distal acquired demyelinating symmetric neuropathy (dads)

Like CIDP, DADS is a demyelinating polyneuropathy. Unlike CIDP, and the previous demyelinating neuropathies, DADS appears to be resistant to immunosuppressive therapy.[36] Clinically, DADS produces an unsteady gait and predominantly distal decreases in sensation and strength. Other features of DADS include an association with an IgM paraproteinemia (two thirds of patients) and a prevalence in men over age 50.[36] Despite the refractory nature of DADS to immunomodulation therapy, many patients receive a trial of one or more agents. The exact reason why DADS is refractory to treatment is not fully understood. Once an explanation is known, it may not only provide insight into the pathomechanism of DADS but also that in other demyelinating neuropathies.

Acute inflammatory demyelinating polyneuropathy (aidp) (guillain-barre syndrome)

Acute inflammatory demyelinating polyneuropathy is an acute, monophasic, demyelinating polyneuropathy. Clinically, it is characterized by symmetric ascending weakness, reduced tendon reflexes, elevated total protein in CSF with albuminocytologic disassociation, conduction block, prolonged f-wave latencies, slowed motor nerve conduction velocities, preceding viral or bacterial infections, and both sensory and autonomic nervous system alterations.[52] Elevated CSF protein occurs in 90% of patients; however, levels may be normal within one week of symptom onset.[37] Cranial nerve palsies occur in 45% to 75% of patients with facial paresis seen in 50% of patients.[37] Acute inflammatory demyelinating polyneuropathy is the most common paralytic disease in Western countries.[37] By definition, progression of symptoms should last less than four weeks. If symptoms progress from four to eight weeks the disease is labeled as a subacute inflammatory demyelinating neuropathy. If symptoms progress past eight weeks the process is referred to as CIDP.

Acute inflammatory demyelinating polyneuropathy is a neurological emergency and can often be life threatening with respiratory compromise and/or autonomic instability. Twentyfive percent of patients with AIDP require assisted ventilation, between 3.5% and 12% of AIDP patients die from complications of the disease, and 62% of patients retain permanent deficits from the disease three to six years after initial onset.[53] The presence of an 80% reduction in sensory and motor action potential amplitudes is associated with poor clinical recovery indicating axonal damage in addition to loss of myelin.[37]

Acute inflammatory demyelinating polyneuropathy is a complex, organ specific, immunemediated neuropathy caused by antiperipheral nerve myelin antibodies that cause demyelination and subsequent axonal damage.[52] The exact mechanisms that underlie this process are not known. It is believed that the complement system, Tand B-cells, anti-i diotypic antibodies, cytokines, and macrophages all play a role in myelin damage with subsequent multifocal demyelination, conduction reduction, weakness and sensory loss.[52] Overall, the pathophysiologic severity of AIDP is thought to be a result of both humoral and cell-mediated immune processes.[52]

The treatment of AIDP involves immunomodulation. Ironically, prednisone has not been shown to be an effective treatment as based on meta-analysis of randomized clinical trials.[54] Plasma exchange is one of the main treatment modalities for AIDP. Plasma exchange is thought to successfully modify humoral processes, although its extended use in AIDP is limited by the necessity of good venous access and resource availability.[52] Exchanges of 200–250 mL/kg are commonly used during five apheresis treatments given over 7 to 14 days.[52] Well-designed clinical trials have shown that plasma exchange decreases patient requirement for assisted ventilation, improves the course of muscular weakness, improves overall disability grade, and shortens the time to unassisted ambulation.[52] A meta-analysis of six randomized clinical trials showed plasma exchange to be superior to supportive care alone. In addition, plasma exchange was found to be most effective when given within seven days of symptom onset.[55] The use of continuous flow machines and albumin as the substitute solution also improved outcomes with apheresis.[55] In severe AIDP, four treatments were found to be as effective as six, although clinically five to six exchanges are often utilized.[55,37]

Intravenous immunoglobulin, another effective treatment of AIDP, facilitates the removal of antibodies that block conduction and other circulating factors. Meta-analysis of past clinical trials has shown that IVIG compared to no treatment decreases disability at four weeks.[53] Dosing schedules of IVIG vary; 2g/kg total dose (divided over two to five days) is commonly used.[52] Treatment should be utilized as soon as AIDP is recognized.

It is unclear if IVIG has better efficacy in AIDP than plasma exchange. Intravenous immune globulin started within two weeks of symptom onset is as likely to quicken recovery as plasma exchange, and has a higher rate of completion of the full course of therapy. Some reports suggest that despite similar efficacies, IVIG may ultimately have a lower complication rate, and that this should encourage its use over plasma exchange in nonambulatory AIDP patients.[52] However, IVIG may worsen certain medical conditions such as comorbid hyperviscosity, congestive heart failure, chronic renal failure, and congenital IgA deficiency. In these circumstances plasma exchange is a better choice of treatment.[37] The combination of IVIG given after a full course of plasma exchange has not shown any additional benefit over one of these treatments alone.[53]

A newer approach to the acute treatment of AIDP involves the filtration of CSF. A limited study comparing this new approach to plasma exchange showed comparable efficacy; however, much more evaluation of this technique is needed before it can be considered as an alternative to either plasma exchange or IVIG.[56]

Acute inflammatory demyelination polyneuropathy variants

The variants of AIDP are an understudied group of conditions differentiated either by electrodiagnostic testing (in the case of acute motor axonal neuropathy and acute motor sensory axonal neuropathy) or by their unique clinical presentation (as in Miller Fisher syndrome). Like AIDP, the variants are thought to result from an immune-mediated pathomechanism. Variants of AIDP are usually treated with the same therapies used for AIDP with apparent but unproven efficacy.[20] Large multicenter clinical trials are needed to determine the most effective therapies for these conditions.

Acute motor axonal neuropathy (aman)

Acute motor axonal neuropathy is a pure motor form of AIDP that is common in both children and adults. This condition causes symmetric limb weakness, areflexia, facial diplegia, oropharyngeal weakness and respiratory muscle weakness while sparing sensory systems and extraocular muscles.[57] Acute motor axonal neuropathy may occur in epidemics, as seen during the summer months in northern China, or may be spontaneous.[37] Campylobacter jejuni infections are often linked to AMAN, and are found in 76% of Chinese patients with this disease.[37] Electrodiagnostic testing shows reduced amplitudes of the compound muscle potentials, but in contrast to typical AIDP, (Guillain-Barre syndrome) increased motor latencies, reduced conduction velocities, and reduced amplitudes of the sensory potentials do not usually occur. Histologically, AMAN exhibits a macrophagemediated cellular damage without lymphocytic infiltrates.

Acute motor sensory axonal neuropathy (amsan)

Acute motor sensory axonal neuropathy is an AIDP variant with rapid progression, muscle wasting, and respiratory insufficiency. Without electrodiagnostic testing, this condition is indistinguishable clinically from acute severe episodes of AIDP.[57] Electrodiagnostic testing shows a reduction in amplitudes of both compound motor action potential and sensory nerve action potentials in the presence of electromyographic fibrillation potentials.[37] Unlike AIDP, no demyelinating features are present.[37] The prognosis of AMSAN is worse than that of AIDP with a more severe clinical course and smaller degree of clinical recovery. Acute motor sensory axonal neuropathy is thought to be mediated by a macrophage process while lymphocytic infiltrates to not occur.[35,37]

Miller fisher syndrome (mfs)

Miller Fisher syndrome is a demyelinating neuropathy characterized by ophthalmoplegia, limb ataxia, and areflexia. Electrodiagnostically, sensory nerve action potentials are typically reduced while F-wave latencies and motor conduction studies are usually normal.[37] Serum IgG antibodies to ganglioside GQ1b are typical in the acute phase of this

disease. Compared to AIDP, the prognosis is better with MFS with recovery expected after a mean of 10 weeks.[37]

Representative Immune Modulating Medications

Corticosteroids

Corticosteroids remain the cornerstone of immunomodulation due to their effectiveness, affordability, and history of use. Corticosteroids are effective treatment for neuromuscular diseases such as MG, DM, PM, chronic inflammatory demyelinating polyneuropathies, leprosy, and Duchene muscular dystrophy.

Common side effects of corticosteroids include hypertension, cushingoid features, an increased risk of infection, bone demineralization, insomnia, cataracts, glaucoma, personality changes, weight gain, hypertrichosis, hyperglycemia, hyperlipidemia, psychosis, and gastric ulcers. Additionally, high-dose, long-term corticosteroid use in the context of inactivity may cause type-2 muscle fiber atrophy and subsequent weakness.[23] In patients with an inflammatory myopathy this side effect (steroid myopathy) may be differentiated from a flare of the inflammatory myopathy by the lack of pronounced CK elevation, lack of acute membrane irritability on electromyographic studies and the presence of cushingoid features; however, the final differentiation between a flare of an inflammatory myopathy and the presence of steroid myopathy requires tapering in the dosage of corticosteroid therapy.[23]

Measures should be taken to monitor and treat the side effects of prednisone. Regular physical activity as the disease permits should be encouraged to curb weight gain. Aquatic therapy may be especially helpful. Bone density should be monitored periodically through the use of Dexa scans (dual energy x-ray absorptiometry). Some physicians advocate the prophylactic use of weekly bisphosphonate to prevent osteopenia, while others utilize this only in the context of osteopenia by Dexa scan. In a trial of 477 patients receiving glucocorticoid therapy, patients treated with 5 mg or 10 mg per day of the biphosphonate alendronate had lumbar bone density increases of 2.1% and 2.9% respectively with fewer vertebral fractures seen in these two groups.[58] Other measures used to insure bone health include administering vitamin D and calcium supplements. Patients who develop gastric reflux as a result of corticosteroid therapy benefit from treatment with proton pump inhibitors, H2 (histamine) receptor blockers, or over the counter Tums. Blood pressure, serum glucose levels, and serum potassium levels should be monitored and corrected in patients receiving corticosteroid therapy. Regular clinical examinations should include evaluations for cataract formation and glaucoma. Intractable side effects from corticosteroid use may provide reason to utilize other immunomodulating medications as treatment.

Methotrexate

Methotrexate is an immunomodulating agent that acts as a folate antimetabolite and inhibitor of DNA synthesis.[59] Methotrexate irreversibly binds to dihydrofolate reductase, inhibiting the formation of reduced folates and thymidylate synthetase, resulting in inhibition of purine and thymidylic acid synthesis.[59] Risks of use include: alopecia, stomatitis, pulmonary fibrosis, teratogenicity, oncogenicity, risk of infection, bone marrow suppression, renal toxicity, and liver toxicity.[23] Patients receiving methotrexate should receive folic acid supplementation. In addition, patients should have liver function and blood counts monitored frequently. Methotrexate is used commonly in inflammatory myopathies and MG. The riskversus-benefit of methotrexate in patients having both inflammatory myopathy and interstitial lung disease should be seriously considered before initiating methotrexate therapy, given the potential of developing pulmonary fibrosis as a side effect of this medication.

Azathioprine

Azathioprine is another immunosuppressive antimetabolite. Although the exact mechanism of action is not known, it is thought to antagonize purine metabolism, inhibit synthesis of DNA, RNA, and proteins, and interfere with cellular metabolism and mitosis.[60] Delayed hypersensitivity and cellular cytotoxicity tests are suppressed to a greater degree than is the antibody response.[61] Azathioprine accumulates intracellularly and its onset and peak therapeutic efficacy as well as its loss of efficacy often takes several months. In neuromuscular medicine, azathioprine is commonly used in diseases such as DM, PM, MG, and chronic inflammatory polyneuropathies.

Side effects of azathioprine include fever, abdominal pain, nausea, vomiting, anorexia, bone marrow suppression, hepatic toxicity, pancreatitis, teratogenicity, oncogenicity, and increased risk of infection.[23] Serum azathioprine levels, blood counts, platelet counts, and liver function should be monitored.[25] At dosages of 2–3 mg/kg, white blood cells counts may fall to 4,0000 with lymphocyte counts reduced to 750 cells/mL.[25] Neutrophil counts less than 1,000/ mL or platelet levels lower than 150,000/ml are reasons to reduce or discontinue treatment.[25] In a study evaluating the side effects of azathioprine in neuromuscular patients, 39% developed hematological toxicity, 12% systemic toxicity, and 9% developed hepatic toxicity.[62]

Mycophenolate mofetil

Mycophenolate mofetil is an immunosuppressant agent that works by inhibiting the de nova pathway of guanosine nucleotide synthesis.[63] Mycophenolate mofetil has a potent cytostatic effect on lymphocytes and inhibits proliferative responses of Tand B-lymphocytes to both mitogenic and allospecific stimulation.[63] Mycophenolate mofetil also suppresses antibody formation by B-lymphocytes and interferes with the recruitment of leukocytes into sites of inflammation.[63] This medication is used in MG and individual case reports exist demonstrating its benefit in both inflammatory myopathies and CIDP.[64,38] Side effects include: diarrhea, nausea, vomiting, headache, bone marrow suppression, hypertension, tremor, infection, neoplasia, and teratogenicity.[23] Standard dosing is 1g by mouth twice daily with care given to avoid higher dosing in patients with renal failure.[23]

Intravenous immunoglobulin (ivig)

Intravenous immunoglobulin is a sterile, highly purified polyvalent antibody product containing concentrated IgG antibodies.[65] Cold ethanol fraction of human plasma is used to make each dose of IVIG.[20] IVIG is used in many neuromuscular disorders including: DM, PM, MG, AIDP, CIDP, and may play a role in more obscure conditions such as MMN, neuropathy associated with anti-MAG antibodies, LewisSumner syndrome, and paraneoplastic neuropathies.[66] The exact mechanism of effect on neuromuscular disease is not clear, although IVIG is thought to modify the immune system through complement inactivation, neutralization of idiotypic antibodies, cytokine inhibition, and saturation of Fc receptors on endoneurial macrophages.[67] An alternative mechanism of action is that excessive IgG exceeds the ability of specialized receptors FcRn to endocytose the IgG causing the body to accelerate the breakdown of IgG by diverting it to lysosomes.[53] Intravenous immunoglobulin also contains neutralizing antibodies against bacterial or viral superantigens that may ultimately inhibit cytotoxic T-cells.[52]

Side effects of IVIG include rash, aseptic meningitis with transient meningeal irritation, cerebral infarction, headache, myalgia, fever, chills, nausea, vomiting flushing, hypotension, hypertension, hemolytic anemia, transient lymphopenia, transient thrombocytopenia, skin reactions, alopecia, and renal failure.[23,66] Obtaining baseline electrolyte studies prior to initial administration is necessary. It is also reasonable to check patients for IgA deficiency before giving IVIG given the increased risk of anaphylactic hypersensitivity in patients with low IgA levels. Intravenous immunoglobulin should be given slowly, with the directions from each manufactured sample followed to limit the chance of side effects. Corticosteroid treatment or nonsteroidal anti-inflammatory drug (NSAID) use before treatment may reduce the occurrence of IVIG induced headache.[66]

Plasma exchange (pe)

Plasma exchange is thought to ameliorate certain neuromuscular diseases through the removal of immune-mediated complexes, activation of the complement system, and removal of tissue bound autoantibodies.[42,52] Both centrifugal blood separators and membrane separators are used to implement this process. Centrifugal blood separators are more commonly used, and require anticoagulation with citrate, which may increase the risk of bleeding.[52] Plasma exchange is utilized for MG, and both acute and chronic demyelinating polyneuropathies. The disadvantages of PE are its short lived effects, high cost, invasiveness (it usually requires a central line or large bore access), and limited availability. Experts in pheresis must be available to perform and supervise treatment. Side effects include lightheadedness, iron supplementation correctable anemia,

and paraesthesias.[42] Contraindications include coagulopathy, thrombocytopenia, septicemia, active bleeding, and severe cardiovascular instability.[42,37]

Cyclophosphamide

Cyclophosphamide is a nitrogen mustard agent that alkylates and crosslinks DNA. Cyclophosphamide has been used in steroid resistant MG, DM and PM with varying results. Along with IVIG, cyclophosphamide also serves as a principle treatment of MMN.[37]

In one study of seven patients with inflammatory myopathy treated with cyclophosphamide, five patients demonstrated modest improvement in strength, two experienced serious infections, and another died, possibly related to complications from cyclophosphamide.[68] Careful risk-versus-benefit analysis is necessary when prescribing and monitoring treatment with cyclophosphamide.

Side effects include gastrointestinal symptoms, bone marrow toxicity, alopecia, hemorrhagic cystitis, teratogenicity, sterilization, increased risk of infection, and dose-related increased incidence of secondary malignancies.[23] High fluid intake is necessary to reduce the risk of hemorrhagic cystitis, and frequent monitoring of the blood count and urinalysis is needed to identify adverse effects early.[23]

Chlorambucil

Chlorambucil is an alkylating nitrogen mustard agent that crosslinks DNA. It has been used effectively with or without prednisone for recalcitrant inflammatory myopathies.[69] Possible side effects include malignancy, bone marrow suppression, liver toxicity, hypersensitivity reaction, Stevens-Johnson syndrome, gastrointestinal disturbances, infection, and teratogenicity.[23] Blood counts and liver function should be monitored with this medication.

Cyclosporine

Cyclosporine is an immunosuppressant that inhibits T-cell lymphocytes. It is used in MG, as a third line agent in PM and DM, and has shown some benefit in limited studies of Duchene muscular dystrophy.[70] Possible side effects include renal toxicity, hypertension, electrolyte imbalance, gastrointestinal upset, hypertrichosis, gingival hyperplasia, oncogenicity, tremor, and infection.[23] Dosages should be adjusted to obtain serum levels of 50–200 mg/mL.

Tacrolimus

Tacrolimus is a T-cell lymphocyte inhibitor much like cyclosporine, which is utilized in DM and PM and occasionally in MG. Its side effect profile is similar to that of cyclosporine.[23]

Tumor necrosis factor-α blockers (etanercept and infliximab)

Etanercept and infliximab specifically bind to tumor necrosis factor (TNF) while blocking its interaction with cell surface TNF receptors and preventing its role in normal inflammatory and immune responses.[71,72] Tumor necrosis factor-α, when not inhibited, acts on the immunologic system by inducing proinflammatory cytokines interleukins (IL)-1 and 6, enhancing leukocyte migration, activating neutrophil and eosinophil functional activity, inducing acute phase reactants, as well as degrading enzymes produced by synoviocytes and chondrocytes.[72] Case reports exist stating the benefit of these medications in PM and DM as well as CIDP and CIDP variants.[23,38] This class of medication may cause life threatening infections, hematological suppression, exacerbation of heart failure, hypersensitivity reactions, malignancies, lupus-like syndromes, optic neuritis, seizures, and vasculitis.[71,72]

Rituximab

Rituximab is a monoclonal antibody against the B-cell epitope CD20.[35] It has been used in MMN with limited effects and has potential as an immunomodulating therapy for other neuromuscular diseases. The possible side effects are many, and include hematological suppression, hypotension, cardiac failure, pulmonary symptoms, gastrointestinal symptoms, systemic fevers, and rash.[73]

Thalidomide

Although infamous for its tetratogenic properties, this medication has gained acceptance for its use in leprosy, discoid lupus, and certain cancers. Thalidomide is thought to suppress excessive TNF-α production and impair leukocyte migration though its exact mechanism of action is not fully understood.[74] It is imperative that it not be given to pregnant women or woman capable of becoming pregnant given its human teratogenicity. Side effects include peripheral neuropathies, thrombotic events, orthostatic hypotension, neutropenia, rash, seizures, and hypersensitivity reactions.[74]

Neuromuscular junction agents

The neuromuscular junction is anatomically composed of the presynaptic region containing the nerve terminal with its packets of acetylcholine, the synaptic space with the synaptic basement membrane, and the postsynaptic region containing the junctional folds and acetylcholine receptors. Acetylcholine is released from the nerve terminals into the synaptic space and it traverses the space to bind to its postsynaptic receptors in the junctional folds on the endplate of the muscle fiber. Ultimately, this binding produces an ionic current, depolarization, muscle action potential and subsequent contraction of the muscle fiber.[75] Neuromuscular junction disorders occur when any part of these mechanisms are disrupted. The classic model of neuromuscular junction disease remains MG. However, other disorders, such as Lambert Eaton myasthenic syndrome, botulism, tic paralysis, and the congenital MG syndromes also benefit from agents that enhance the release and action of acetylcholine on its receptor.

Representative Diseases That Benefit from Medications Affecting the Neuromuscular Junction

Myasthenia gravis

The symptoms of MG can be improved through the use of cholinesterase inhibitors. Patients often report improved strength and reduced fatigue, diplopia, and bulbar findings with use of these medications. The commonly used oral pyridostigmine is typically started at 30mg per day in adults with a titration in frequency to three to four times a day. In children, the dosages are typically lower, starting at 1.0 mg/kg.[76] These medications have the potential to produce a cholinergic crisis in which weakness, diarrhea, cramps, lacrimal discharges, increased salivation, miosis, nausea, and abdominal pain are the hallmark features. It is imperative that the clinician acknowledge the symptoms of acetylcholinesterase toxicity in order to make the distinction between this entity and a myasthenia exacerbation. Immunomodulating treatment has reduced the reliance on medications that inhibit cholinesterase. See also the previous section, Immune Modulating Medications, for clinical information about MG.

Congenital mg

Congenital MG is a heterogeneous group of diseases caused by gene mutations affecting the protein subunits of the receptor for acetylcholine, other proteins in the postsynaptic region, as well as proteins in the presynaptic region of the neuromuscular junction.[77] The genetic etiologies of these diseases are varied and may cause a choline acetyltransferase deficiency, a reduction in quantal acetylcholine release, an end-plate acetylcholinesterase deficiency, a prolonged opening of acetylcholine receptor channels (slow-channel syndrome), a primary acetylcholine receptor deficiency with or without minor kinetic abnormalities (PARDWOWMKA), or a plectin deficiency.[78] In general, during

early childhood these diseases present with fatigable weakness, dysfunction of the ocular, bulbar, and limb muscles, a decremental response to 3-Hz repetitive stimulation, and the absence of acetylcholine receptor antibodies. Unlike MG, the congenital MG syndromes are not autoimmune disorders and typically do not respond to immunosuppressive therapies. Except for slow-channel syndrome and end-plate acetylcholinesterase deficiency, congenital myasthenia syndromes benefit symptomatically from acetylcholinesterase inhibitors.[78] In slow-channel syndrome, a class 1a antiarrhythmic agent, quinidine, was found to provide clinical benefit through its action of correcting a state of prolonged channel opening.[79] Additionally, 3,4-DAP has shown symptomatic benefit in congenital myasthenia syndromes both as an add-on therapy to anticholinesterase treatment in PARDWOWMKA and as a primary therapy in plectin deficiency.[78,80]

Lambert-eaton myasthenic syndrome (lems)

Lambert-Eaton myasthenic syndrome is a paraneoplastic disorder caused by autoantibodies that lead to a reduction in the release of acetylcholine from the presynaptic nerve terminals through interference with the function of their voltage-gated calcium channels.[81] On neurological examination this disease reduces tendon reflexes and causes fatigable weakness, both of which may improve immediately after a series of vigorous muscle contractions or more prolonged exertion.[82] Medications to treat LEMS include 3–4-diaminopyridine (3–4DAP), guanidine, acetylcholinesterases, and immunomodulating agents (including: PE, IVIG, corticosteroids, azathioprine, cyclosporine, and mycophenolate). In patients with persistent, disabling weakness, long-term treatment options include prednisone (60–80 mg/day) and azathioprine (2–3 mg/kg/day) in conjunction or independently.[83] Cyclosporine (5–6 mg/kg/ day divided twice daily) may prove helpful in patients who do not respond to either of these treatments.[84] Pyridostigmine bromide has been shown to improve the symptoms of dry mouth without clear improvement of strength. Intravenous immune globulin and PE may markedly increased strength in LEMS patients. However, these effects are only transient, and repeated use of these therapies is necessary to maintain the benefit.

Guanidine is an effective add-on medication to pyridostigmine in LEMS, but caution is needed because of its toxicity. Guanidine dosages of 375–1000 mg/day with pyridostigmine use may increase functional status and strength in LEMS patients.[85] Unfortunately, up to 50% of patients develop gastrointestinal side effects and more severe side effects such as, depression of the bone marrow, liver dysfunction, renal insufficiency, tremor and ataxia may occur.[85]

Botulism

Botulism is a disease that compromises the normal release of packets of acetylcholine at the neuromuscular junction and is caused by the toxins produced by the anaerobic grampositive bacillus clostridium botulinum. Botulism affects 70 to 100 people each year in the United States.[86] Clostridium botulinum is a naturally occurring pathogen that exists in contaminated food sources, or in the dust from endemic areas. Five forms of botulism exist: (1) wound, (2) foodborne, (3) infantile, (4) adult infectious, and (5) inhaled.[87,88] Botulism may occur through exposure to a natural form, or through unintentional botulinum toxin overdose. The incidence of infantile botulism can be reduced through proper processing of canned foods and the avoidance of honey consumption by infants. Used properly, botulinum toxin is an effective treatment for cervical torticollis, strabismus, blepharospasm, migraine headache, chronic low back pain, stroke, traumatic brain injury, cerebral palsy, achalasia, and focal dystonia.[87] The incidence of botulism toxin overdose can be avoided through careful monitoring and titration schedules during the course of treatment.

The toxin of botulism affects the voluntary motor and autonomic systems by preventing acetylcholine-containing vesicles from joining with peripheral presynaptic terminal membranes at the neuromuscular junction.[87,88] Specifically, the botulinum toxin enters neurons by endocytosis after which the light chain of the toxin cleaves sites on specific proteins preventing completion of synaptic fusion and subsequent acetylcholine release.[87]

Clinical features of infant botulism include: hypotonia, weakness, diminished gag reflex, ptosis, minimally reactive mydriasis, constipation, ophthalmoparesis, weak suck, and a weak cry.[86,89] Adult patients may present with an acute, afebrile, symmetrical descending flaccid paralysis with associated ptosis, diplopia, blurred vision, dysarthria, dysphonia, dysphagia and poorly reactive pupils.[90] Reflexes are often absent, and sensory symptoms are typically spared. Diagnosis is based on clinical features and supported by the electrodiagnostic findings of persistent (>2 min) postactivation facilitation after isometric exercise or high frequency (20–50 Hz) repetitive stimulation, decreased compound action motor potential amplitudes, and the lack of postactivation exhaustion.[91] Single fiber EMG may show increased jitter and blocking that becomes less marked after activation.[92] The diagnosis of botulism may be confirmed by the presence of toxin and spores in fecal samples. Unfortunately, fecal analysis is lengthy and the results are often not available to assist in guiding early decisions about treatment.

Supportive care is the mainstay of treatment for botulism. Patients may have reversible respiratory insufficiency and assisted ventilation is necessary until recovery occurs. A human botulism immune globulin (BIG) is available for treatment of infantile botulism. In a review of 39 cases of infantile botulism, patients who received IV BIG had shorter hospital courses by an average of 17 days.[86]

A trivalent antitoxin is used for treatment of older patients with botulism. In a study of 132 patients with foodborne botulism type A infections, patients receiving a trivalent equine antitoxin had lower fatality rates and shorter hospital stays compared to controls.[93] Likewise, patients who received the antitoxin within 24 hours had a shorter disease course, (although similar fatality rate) compared to those who received the toxin at a later time.[93]

The role of antibiotics in botulism is controversial; however, in isolated wound botulism, penicillin or metronidazole is thought to be beneficial.[90] Antibiotics are not recommended in infantile botulism due to a proposed increase in toxin availability after lysis of intraluminal botulinum organisms.[94]

Guanidine, a stimulator of acetylcholine release from nerve endings, has also provided benefit by improving ocular function and limb strength, but no substantial benefit to respiratory function has been reported.[95,96]

Medications Affecting Transmission at the Neuromuscular Junction

Acetylcholinesterase inhibitors

This class of medications is sometimes used in MG and other neuromuscular junction disorders for symptomatic benefit. These medications act by inhibiting the hydrolysis of acetylcholine at the neuromuscular junction.[2] Medications in this class include pyridostigmine, neostigmine, and the shorter acting edrophonium. Although intravenous, intramuscular, subcutaneous, and oral preparations are available, the use of injectable forms of antiacetylcholinesterase medications has become relatively uncommon. The emergence of PE and IVIG as treatments for myasthenic crisis and worsening of symptoms along with the availability of excellent intensive care support for patients with loss of effective swallowing and ventilatory power have largely bypassed the need for giving these antiacetylcholinesterase medications by nonoral routes of administration. An additional concern involved in using injectable forms of antiacetylcholinesterase medications is the nonequivalency between dosages of oral and injectable forms. If the same total dosage as is usually taken by mouth is given to the patient by injection, it will produce severe, potentially life-threatening toxicity.

Because of the availability of other treatments for acute loss of swallowing in MG it is usually preferable to hold all antiacetylcholinesterase treatment until the inpatient myasthenic patient regains their ability to swallow safely. At that point antiacetylcholinesterase therapy can be reinitiated, often at a lower dosage than prior to the episode of worsening. The total dose and frequency of administering cholinesterase inhibitors directly relates to their half lives and the dosage is titrated or tapered based on the perceived benefit of strength and side-effect profile. The side effects of acetycholinesterase inhibitors are due to excessive cholinergic activity. These symptoms include: abdominal cramps, vomiting, diarrhea, nausea, muscle twitches, fasciculations, and increased saliva production.[2]

3,4-Diaminopyridine (3,4-dap)

Aminopyridines increase the release of acetylcholine from the presynaptic nerve terminal. Despite not being approved in the United States for this purpose, 3,4-DAP has shown clear benefit in safely improving strength, and autonomic symptoms in LEMS.[97,98] Additionally, 3,4-DAP improves neuromuscular transmission in myasthenia patients when given in conjunction with pyridostigmine. However, the lack of FDA approval, and abundance of other effective therapeutic agents in MG limits its clinical use in this

disorder.[99]

The side effects of 3,4-DAP include perioral and distal paraesthesias and occasionally epileptic events.[97] Nonetheless, 3,4-DAP has a therapeutic advantage over 4-aminopyridine in that it has lesser side effects involving the CNS and leads to fewer seizures at therapeutic levels.[97] Effective dosage schedules of 3,4-DAP vary. Some trials have utilized 20 mg given three times a day, while other trials have titrated patients up to a total of 100 mg a day with higher risks of seizure.[97,98] It has been suggested that 3,4-DAP may have beneficial effects in congenital MG; however, further studies are necessary given the diversity of the congenital MG syndromes and the small number of clinical trials available to assess the efficacy of various treatments.[100]

In animals, 3,4-DAP can delay the onset of paralysis following the administration of botulinum neurotoxin type A in phrenic nervehemidiaphragm preparations.[101] In humans the effects of 3,4-DAP was studied in a 31 yearold with type A botulism. The results of this study showed no clinical improvement with this medication.[102] Another case series showed dramatic reversals of peripheral paralysis with 4-aminopyridine in patients exposed to botulinum type E; however, these results were offset by the limited improvement in respiratory function, the occurrence of seizures, and the transient (less than four hours) nature of the benefits.[103]

Guanidine hydrochloride

Guanidine is a medication thought to increase release of acetylcholine from the presynaptic nerve terminal.[92] There have been many incidental reports of the effectiveness of guanidine in both botulism and Lambert-Eaton myasthenic syndrome.[95] After botulism exposure, improvement in strength has been reported in both the limb and ocular muscles.[95] Unfortunately, a subsequent double-blind, crossover study of 14 patients with type A botulism did not show any improvement in recovery rate after use of this medication.[104]

The side effects of guanidine hydrochloride include dose and time related bone marrow suppression, renal insufficiency, severe gastrointestinal symptoms, hepatic toxicity, fainting spells, tremor, ataxia, and distal paraesthesias.[92,85] Because of its toxicity guanidine is a second or third choice in the treatment of LEMS.[92,85]

The hematological side effects of guanidine hydrochloride occur early in the course of therapy and may be reversed with reduced or discontinued use.[85] Frequent blood tests are required during the first months of treatment.

Glutamate inhibiting agents

This section will focus on two glutamate inhibiting agents: (1) riluzole, a glutamatergic modulator that has been shown to extend survival in amyotrophic lateral sclerosis (ALS), and (2) the combination therapy dextromethorphan hydrobromide and quinidine sulfate, a N-methylD-aspartic acid (NMDA) receptor antagonist and glutamate inhibitor coupled with a P450 inhibitor (quinidine sulfate) that reduces the pseudobulbar effects commonly seen in amyotrophic lateral sclerosis (ALS) patients.

Representative Disease That Uses Glutamate Inhibiting Agents

Amyotrophic lateral sclerosis (als)

Amyotrophic lateral sclerosis is a progressive neuromuscular disease that affects both the upper and lower motor neurons. Its clinical features include progressive weakness, atrophy, fasciculations, spasticity, cramps, pseudobulbar signs, and hyperreflexia.[105] The most common presenting symptom in ALS is weakness of a single limb associated with bulbar symptoms. This combination of symptoms occurs as the presenting complaint in 25% of patients.[106] The mean time to death from symptom onset is approximately three years with a minority of patients living beyond 10 years.[105] Due to the poor prognosis of the disease it is imperative that mimicking diseases such as compressive cervical myelopathies, primary muscles diseases and peripheral neuropathies (such as MMN) be excluded before making the diagnosis.[106] Research criteria have divided groups into definite, probable, possible, and suspected ALS based on the presence or absence of upper and lower motor neuron signs in four body areas: bulbar region, cervical region, thoracic region and lumbosacral region.[105] Classic electrodiagnostic features of ALS include normal sensory nerve action potentials, normal to near normal motor conduction velocities, fibrillation potentials and fasciculations in multiple muscles at different locations, and increased duration and amplitude of motor unit potentials.[105] Magnetic resonance imaging (MRI) of the CNS is useful in ruling out other disease processes, and may detect corticospinal tract pathology with diffusion tensor technology, but can not be used in isolation to make the diagnosis of ALS.[105]

Ongoing research continues to attempt to identify treatment(s) that can cure or partly correct the muscle wasting and weakness in ALS. At present, one medication has emerged as a treatment option for respiratory-bulbar weakness. Riluzole, a glutamate inhibitor, has been shown in clinical trials to both extend life expectancy by several months as well as maintain patients at a less severe stage of the disease as compared to controls.[107,108,109] The optimal dose of Riluzole is thought to be 100 mg per day, which may be divided into twice a day dosing.[105] More robust therapies are needed.

Another symptomatic treatment is dextromethorphan hydrobromide combined with quinidine sulfate for pseudobulbar symptoms in ALS. Dextromethorphan hydrobromide is a noncompetitive NMDA receptor antagonist that inhibits glutamate by binding to the phencyclidine site within the receptorassociated ion channel and subsequently limits glutamate-mediated calcium influx through the channel.[110] Dextromethorphan is also hypothesized to inhibit presynaptic release of glutamate.[111,112] Treatment trials were originally performed on dextromethorphan alone to determine if it could attenuate any of the manifestations of ALS. One double-blind, placebo-controlled trial failed to demonstrate any beneficial effects.[113] It was theorized that the lack of observed benefit was secondary to the rapid metabolism of dextromethorphan hydrobromide.[114] To this end, quinidine sulfate, a selective CYP2D6 inhibitor was added to dextromethorphan hydrobromide to reduce its rate of inactivation. The result is a combination therapy (30 mg of each medication given twice daily) that has improved the quality of life and quality of relationship scores in ALS while reducing the pseudobulbar symptoms (emotional outbursts not corresponding to a patients mood) that are commonly present in ALS.[110,115]

Representative Glutamate Inhibiting Agents

Riluzole

Riluzole is a modulator of glutamatergic transmission that has been shown to have limited benefit in extending lifespan (approximately two months) in ALS patients.[107,108,109] The high levels of glutamate found in the CSF of ALS patients has caused some to speculate that glutamate, an excitatory neurotransmitter, produces or augments the cell damage seen in ALS.[116] Glutamate is proposed to be toxic through the activation of calcium-permeable receptors and/ or voltage-gated calcium channels with resulting elevated free calcium levels.[117] It is yet to be determined if the antiglutamate effects of riluzole are truly the mechanism by which ALS patients gain the modest benefit it provides. Other antiglutamatergic medications, such as, lamotrigine, branched-chain amino acids, and dextromethorphan, have not shown comparable effects on the course of ALS.[118,119] Common side effects of riluzole include nausea, asthenia, and elevated liver enzyme levels.[108] Liver function tests should be monitored with use of this medication.

Dextromethorphan hydrobromide (dm) and quinidine sulfate (avp-923)

Dextromethorphan hydrobromide is a noncompetitive NMDA receptor antagonist that also serves as an inhibitor of neuronal actions of glutamate.[110] DM may also modulate dopamine release in the mesolimbic pathway.[110] Quinidine sulfate is a selective CYP2D6 inhibitor capable of reducing dextromethorphan metabolism. The combination therapy has been found to reduce the symptomatic pseudobulbar affect in ALS, multiple sclerosis, and may have a positive effect on pain in patients with diabetic peripheral neuropathy.[110,120,121]

Dextromethorphan is a common over the counter agent often used as a cough suppressant. Its side effects include dizziness, fatigue, headache, nausea and somnolence.[110] Quinidine sulfate is a class 1a antiarrhythmic medication. There are many potential side effects of these class of medications and they include QTc prolongation,

lightheadedness, gastrointestinal symptoms, hematologic alterations (including bone marrow suppression), and cardiac arrhythmia.[122,123]

Vitamin supplements

A variety of neurological disorders with neuromuscular manifestations can occur with vitamin and/or nutrient deficiencies. Occasionally, supplements themselves can produce neuromuscular manifestations. Examples of this include neuropathies with excessive pyridoxine supplementation and malabsorption of vitamin K and essential fatty acids leading to ataxias with excessive use of vitamin E. Normal physiologic function of the neuromuscular system requires set levels of essential nutrients in the blood. In clinical cases, malabsorption, deficient diets, drug interference, liver or kidney dysfunction, or metabolic dysfunction may hinder the body's ability to effectively utilize these nutrients. The manifestations of vitamin deficiencies are wide spread and may provoke both CNS dysfunction as well as neuromuscular symptoms. It is important to suspect and recognize a vitamin deficiency early in the assessment of a patient, since the progression of symptoms may often be halted, or even reversed at that point with prompt treatment. Delayed diagnosis of many of the deficiencies can lead to permanent loss of function despite restoration of the appropriate level of the deficient nutrient in the blood.

Representative Diseases That Use Vitamin Supplementation

Vitamin b12 deficiency (cobalamin deficiency)

Vitamin B12 deficiency is a common condition that may be present in up to 20% of the elderly population.[124] The etiologies of vitamin B12 deficiency include: cobalamin malabsorption, pernicious anemia, dietary insufficiency, parasitic infiltration, and an inherited malfunction in cobalamin metabolism.[124,125] Vitamin B12 deficiency may present with a macrocytic anemia, atrophic glossitis, diarrhea, myelopathy (often involving the thoracic spinal cord), cerebral dysfunction, visual symptoms (related to optic atrophy) or a peripheral neuropathy. Over time, a B12 deficient peripheral neuropathy can progress from a demyelinative to axonal form.[126] In severe B12 deficiencies, spinal cord alterations produce abnormal findings on physical examination, including spasticity, a positive Romberg sign, weakness, a sensory ataxia, and loss of vibration and position sense.[126]

Diagnosis of B12 deficiency is often obtained through clinical history and by demonstrating a reduction in serum B12 levels. Testing that may suggest the condition includes a mean corpuscular volume (MCV) of >100 fL, an oval macrocytes without stomatocytes on a peripheral blood smear, elevated homocysteine or methylmalonic acid levels, or antiparietal cell and anti-intrinsic factor antibodies suggestive of pernicious anemia.[127] Once the diagnosis of B12 deficiency is obtained, a Schilling test may provide further insight into the etiology of the deficiency. It is imperative to have both methylmalonic acid and homocysteine levels included in the workup of B12 deficiency, as elevations of these metabolites may suggest B12 deficiency even in the context of a normal serum cobalamin level.[127] The exact pathomechanism(s) responsible for the demyelinating and axonal damage within the central and peripheral nervous systems remains to be established. Among the possible factors being considered are a deficiency of S-adenosylmethionine, an elevation of methylmalonic acid, and alterations in cytokines and growth factors.[128]

Treatment of B12 deficiency consists of daily intramuscular injections of 1000 μg/day of cobalamin for one week followed by 1000 μg/week for one month, followed by 1000 μg/month until the deficiency is corrected.[127] In some forms of B12 deficiency, such as, a dietary deficiency, cobalamin malabsorption syndrome, or pernicious anemia, oral supplementation may correct the deficiency. Even in these cases, it is essential that the correction of the low B12 level in the blood is monitored closely. If a normal level of B12 is not established rapidly, intramuscular injections of the vitamin should be given. The oral dosage of vitamin B12 is 1000 μg/day for one month, followed by maintenance doses of 125–500 μg/day for dietary deficiencies and malabsorptive syndromes or continued dosages of 1000 μg/day for pernicious anemia.[124] There are recent studies that indicate that dementia in association with low circulating levels of vitamin B12 may not improve with treatment using oral B12 alone or in combination with folate supplementation.[129,130,131,81] Further research is needed to determine the optimal length of treatment, the full effects of vitamin B12 deficiency, and the ideal end-points for further research.

Folate deficiency

Folate deficiency is caused by reduced absorption, impaired hepatic processing, or disrupted storage. Folate deficiency is commonly known for its causative role in leading to neural tube defects and macrocytic anemia. Depletion of folate occurs with the use of methotrexate, contraceptives, and antiepileptic medications.[132] Case series report an association between folate deficiency and sensorimotor neuropathy.[133,134,135] In these series, benefit was obtained after diagnosis and subsequent folate supplementation.[133,134,135] Further studies are necessary to validate these initial reports and prove that a separate process did not contribute to the diagnosed neuropathies.

Copper deficiency

Copper deficiency is an uncommon, newly recognized cause of a primary myeloneuropathy. Copper deficiency has recently been observed with chronic tube feeding, gastrointestinal surgery (especially gastric bypass), excessive zinc intake, or a deficient diet.[136] A primary dietary deficiency is rare due to the low required daily dose of this element. Clinical manifestations related to copper deficiency include a spastic ataxia, upper motor neuron signs, a positive Romberg sign, an axonal neuropathy, hyperintense T2 signals in MRI of the spinal cord, anemia, and leukemia. Progression of clinical deficits may be reduced by copper supplementation; however, complete resolution of symptoms typically do not occur.[136] An isolated report of recurrent myelopathy in a patient with copper deficiency suggests that higher replacement dosages of copper may reverse symptoms that do not respond to the usually recommended dosage.[137] Serum copper, zinc, ceruloplasmin, and 24 urine copper and zinc levels should be measured if clinical features suggest copper deficiency.[136] Treatment consists of copper supplementation and discontinuation of zinc hypersupplementation if present. Supplementation can be provided thorough daily oral (2 mg/day) dosages or a course of intravenous cupric sulfate 2 mg given daily for five days with adjustments in the schedule of repeated therapy based on clinical and laboratory responses.[138,139]

Beri beri

Beri Beri is a thiamine deficient state that produces a slowly progressive axonal sensorimotor peripheral neuropathy with or without an associated congestive cardiomyopathy. This condition classically has been called, *wet* or *dry* based on the presence or absence of edema. Symptoms consist of lower extremity pain, muscle cramps, distal sensory loss, loss of distal reflexes, and occasional distal extremity weakness.[140] If Beri Beri is clinically suspected, thiamine levels, erythrocyte transketolase activity levels, and pyruvate levels should be checked.[140] Beri Beri is often linked with alcoholism, but may occur from deficient diets or malabsorptive states. Fifty to 100 mg of thiamine supplementation per day is typically utilized in this condition.

Pellagra

Pellagra is a deficiency of nicotinic acid (niacin) that typically affects the gastrointestinal tract, nervous system, and skin. The classic features of pellagra are diarrhea, dermatitis, and dementia, although 4%–56% have a sensorimotor polyneuropathy.[37] Pellagra is most often caused by a niacin deficient diet, but may also occur secondary to malabsorption or alcoholism.

Pyridoxine deficiency

Deficiency of pyridoxine (vitamin B6) can cause a slowly progressive length dependent sensorimotor polyneuropathy. This deficiency may occur during use of isoniazid, hydralazine, pyrazinamide, or penicillamine due to their interference with pyridoxine coenzyme activity.[37,132] Supplementation must be done with extreme care as pyridoxine toxicity may produce a crippling, progressive, large fiber, symmetric, pure sensory axonal neuropathy.[37,141] The clinical features of excessive-dose pyridoxine neuropathy are suggestive of toxicity involving the dorsal root ganglion and may occur at dosages as low as 200 mg per day. Animal models suggest that renal insufficiency and low protein

diet predispose to high-dose pyridoxine toxicity. This information needs to be considered when instituting vitamin replacement treatment for individuals with chronic alcoholism, chronic nutritional deficiency, and chronic intestinal malabsorption. Although the duration of symptoms caused by high-dose pyridoxine toxicity tends to be inversely proportional to the daily dosages used, deficits and abnormal electrophysiological features may be permanent.[141,142]

Representative Vitamin Supplements

Vitamin b12

Vitamin B12 is an essential dietary vitamin utilized for DNA synthesis during chromosomal replication, cell growth, carbohydrate metabolism, hematopoesis, and protein synthesis.[143] The vitamin is produced by microorganisms that grow in the natural environment or human intestinal lumen. The body utilizes gastric acid, proteases, bile, sodium bicarbate, and intrinsic factor to absorb the vitamin.[132] Pancreatic abnormalities, intestinal bacterial or parasitic infiltration, local inflammatory processes such as sprue, anatomical ileal damage, or antibodies to intrinsic factor or parietal cells may affect absorption.[132] This medication is available in an oral form, in an intranasal form, and for injection intramuscularly and subcutaneously. In the treatment of cases of deficiency caused by severe intestinal disease, intramuscular or subcutaneous administration of vitamin B12 are preferred.[132]

Folate

Folate is a nutrient plentiful in fresh green vegetables, liver, and fruit. The recommended daily intake is 400 µg with additional amounts required for pregnant women.[132] It is available in oral and injectable preparations. Alcoholism, jejunal disease, uremia, cancer, or reduced intake may all decrease serum folate levels. Folate supplementation is used in macrocytic anemias. It is also used in pregnant women to reduce the rate of fetal neural tube defects.[144] Side effects of supplementation are infrequent; however, allergic reaction that includes bronchospasm, flushing, malaise, pruritus, and rash may occur.[144] It is imperative that patients with macrocytic anemia be simultaneously evaluated for B12 deficiency, as vitamin B12 deficiency is progressive and will not be corrected by folate supplementation.

Copper

Copper is an essential trace element that is absorbed throughout the entire gastrointestinal tract.[145] It is available in both oral and injectable preparations. Side effects include: hemolytic anemia, hemoglobinuria, jaundice, nausea, vomiting, epigastric pain, headache, dizziness, weakness, diarrhea, and hemochromatosis.[146] Preliminary studies are also available suggesting that cocoa supplementation may serve as another means of replenishing copper deficiency that occurs with chronic tube feeding.[147]

Thiamine

Thiamine is a water soluble vitamin that helps to catalyze the oxidative decarboxylation of pyruvate and alpha-ketoglutarate in the body.[140] High amounts of thiamine exist in legumes, pork, beef, whole grains, yeast, and fresh vegetables.[148] Three weeks without dietary thiamine may produce a deficient state.[148] Oral and injectable preparations are available for use. Thiamine is commonly given to patients as a therapy for suspected Wernicke's encephalopathy, Korsakoff's syndrome, as well as for Beri Beri as described previously. A high carbohydrate diet or intravenous glucose infusion may exacerbate or precipitate Wernicke and Korsakoff syndromes by leading to acute thiamine deficiency in at risk individuals due to thiamine's utilization in carbohydrate metabolism.[141]

Nicotinic acid

Nicotinic acid forms two coenzymes that are utilized for tissue respiration, lipid metabolism, and glycogenolysis.[149] Nicotinic acid can be utilized both for replenishing a deficient state and as a treatment for hyperlipidemia. Nicotinic acid exerts its lipid lowering effect by binding to its receptor on a G-protein coupled site that in turn leads to a decreased level of cAMP, which causes a decrease in lipids.[150] The RDA for nicotinic acid is 19 mg a day for males over age 51 and 15mg per day for women over age 51.[149] An elevation of blood glucose and liver enzymes may occur with niacin therapy, and flushing is its most common side effect.[149]

Pyridoxine

Pyridoxine is a water soluble vitamin available in oral and injectable forms. It is typically utilized in deficiency states related to malnutrition, chemotherapy or abnormalities in absorption.[151] As stated previously, care must be utilized in supplementation given the risk of inducing a large fiber, symmetric, pure sensory, axonal neuropathy.

Enzymatic replacements

While the exact pathomechanisms that cause the disease manifestations in most neuromuscular diseases remain a mystery, some disease processes have been elucidated to the point where a specific alteration can be identified and a treatment initiated. Diseases in which a specific enzyme is absent lend themselves to enzymal replacement therapies. Such therapies are currently used in Pompe disease, Fabry disease, Gaucher disease, and mucopolysaccharidosis type I (Hurler/Scheie disease). Enzymatic replacement therapies are close to being developed for mucopolysaccharidosis II (Hunter disease), mucopolysaccharidosis VI (MaroteauxLamy), and Niemann-Pick disease.[152]

Representative Diseases That Use Enzymatic Replacement

Fabry disease

Fabry disease is an X-linked recessive glycosphingolipid storage disease caused by a deficiency in lysosomal hydrolase alphagalactosidase A.[153] This enzyme deficiency leads to an accumulation of globotriaosylceramide that may lead to renal, ocular, gastrointestinal, dermatologic, cerebral, vascular, cardiac, and neurological symptoms.[154] The neuromuscular features of Fabry disease include a small fiber peripheral neuropathy, paroxysmal distal burning dysesthesias, and episodes of acute incapacitating pain triggered by stress, heat, fatigue, fever, or exercise.[155] Episodes of acute pain start distally with radiation proximally and may last from minutes to weeks.[155] Diagnosis may be obtained by demonstrating a deficiency of alpha-galactosidase A in a patient's tissue.[156] Treatment focuses on pain management, evaluations and ongoing care by subspecialists, and enzymatic replacement therapy of the deficient alpha-galactosidase A enzyme.

Alpha-galactosidase A is safe and beneficial in Fabry disease patients.[154] Intravenous preparations of 0.2 mg/kg given every other week (for a total of 12 infusions) reduce pain severity scores, decrease mesangial widening, increase creatinine clearance, increase body weight and improve cardiac conduction in Fabry patients.[154] Enzymatic therapy also reduces globotriaosylceramide endothelial deposits after 20 weeks.[157]

Acid maltase deficiency

Acid maltase deficiency, also known as glycogen storage disease type II, or Pompe disease (when its onset is in early childhood), is an autosomal recessive disease caused by a deficiency of alpha-glucosidase (GAA).[158] This deficiency causes lysosomal glycogen to accumulate in muscle and other body tissues. The clinical features of Pompe disease include: hypotonia, a profound progressive proximal weakness, a hypertrophic cardiomyopathy with progression to a dilated cardiomyopathy, and an early demise. In the juvenile or adult onset variant of acid maltase deficiency, clinical features may include a slowly progressive (prominently proximal) weakness, and respiratory dysfunction.[158,152,159] Patients with Pompe disease often do not live past a year, whereas the juvenile and adult forms typically do not have cardiac impairment and carry a much longer life expectancy.[152]

Diagnosis of acid maltase deficiency is confirmed through a GAA assay on muscle or cultured skin fibroblasts.[152] Until recently, the mainstays of treatment included physical therapy, prevention of contractures through stretching and braces, diets rich in L-alanine, and respiratory management.[158,152] More recently, the FDA approved the use of an effective enzymatic therapy (rhGAA) that replaces the deficient enzyme directly through intravenous administration.

Infusions of rhGAA cause few severe adverse events and are beneficial in early onset disease with improvements of left ventricular mass, cardiac function, skeletal muscle function and muscle pathology.[160] Investigations have demonstrated that through at least 10 months of treatment, rhGAA infusions maintain left ventricular mass index, fractional shortening, and muscle strength.[161]

In late-onset acid maltase deficiency, patients given weekly infusions of rhGAA have shown stabilization of pulmonary function, reduced fatigue, and at times marked improvement of skeletal muscle function.[162]

Representative Enzymatic Replacements

Alpha-galactosidase a (α-gala)

Alpha-galactosidase A has been found to be both safe and beneficial in patients with Fabry disease.[154] The treatment does cause side effects. One study demonstrated that rigors (48%), fever (24%), headache (17%), chills (14%), hypertension (10%), and pain related to Fabry disease (10%) frequently occur in patients taking this therapy.[157]

Human precursor acid alpha-glucosidase (rhgaa)

Infusion of rhGAA is an effective therapy for both early and late onset acid maltase deficiency. Overall, this treatment appears to be well tolerated. In one study of over 250 separate (5 mg/kg) intravenous infusions, hematologic, liver, and renal function parameters remained within the normal range while rash and associated fever and irritability only occurred with three of these infusions.[163] Serious adverse reactions that have been reported include heart failure, respiratory failure, allergic shock, pneumonia, infections, and fever.[164]

Because of an encouraging benefit-to-riskratio the FDA approved the use of intravenous rhGAA in April of 2006 for treatment of earlyonset acid maltase deficiency.[164]

Preventive vaccines

Disease prevention remains one of the major opportunities for controlling neuromuscular diseases. Vaccinations for both poliomyelitis and diphtheria have led to drastically reduced rates of occurrence for both of these infection-mediated neuromuscular diseases. In the future there may be opportunities to develop vaccine therapies for other infection-mediated neuromuscular disorders and perhaps for several noninfection related neuromuscular diseases.

Representative Diseases That Use Preventative Vaccines

Poliomyelitis

Poliomyelitis is a fecal-to-oral transmitted enteroviral disease that causes fever, fatigue, headache, vomiting, meningismus, and peripheral limb pain.[165] One out of 200 patients infected with poliomyelitis develops an irreversible paralysis.[165] The neuromuscular weakness of poliomyelitis usually occurs at the time of initial illness and most frequently at the period of fever resolution.[166] Severe muscle and back pain typically occur at the outset of weakness and loss of tendon reflexes develop hours to days later.[166] Bulbar and diaphragmatic weakness may occur, requiring life-saving mechanical ventilation. Patients with a prior poliomyelitis infection may also have a late progression of their disease decades after its onset. This syndrome is known as postpolio syndrome (PPS) and usually develops very gradually. Its manifestations are usually protean and are easily attributed to other causes until the critical history of a prior polio infection or exposure is apparent. Common initial manifestations include muscle pain, atrophy, generalized fatigue, dysphagia, respiratory insufficiency, cramps, fasciculation, sleep abnormalities and cold intolerance.[166] Primary prevention through vaccination remains the most essential pharmacologic intervention for both primary poliomyelitis and secondary PPS.

Diphtheria

Diphtheria is an infectious disease caused by the gram-positive pathogen corynebacterium diphtheriae (*c. diphtherias*). This disease is transmitted through respiratory secretions and presents with sore throat, fever, dysphagia and malaise. Up to two-thirds of cases may have a tonsillopharyngeal infection with or without other respiratory tract infections.[167] Gray spots or the classic pharyngeal pseudomembrane may occur in approximately 28% of the patients, as can punched-out ulcerations on the skin in the cutaneous variant of *c. diphtheria*.[167,168] Neuromuscular manifestations of diphtheria occur in 75% of all severe cases and are secondary to a toxin produced as an extracellular polypeptide of c. diphtheriae.[167] Neuromuscular symptoms include: bulbar dysfunction; pharyngeal, oculomotor, and ciliary muscle paralysis; glove and stocking paraesthesias; and weakness that spreads from proximal to distal muscles.[167] Weakness often presents months after the onset of the initial infection and may produce total paralysis.[169] Nerve conduction studies, while initially normal, may eventually demonstrate a demyelinating neuropathy with decreased nerve conduction velocities and delayed F-wave latencies. Diphtheria toxin produces an almost pure form of demyelinating neuropathy. Diagnosis is obtained on clinical grounds, although culture of throat swabs may confirm the presence of *c. diphtheriae* in 56% of patients.[168] Electrodiagnostic features may also aid in making a diagnosis, although results can be similar to those seen in acute inflammatory demyelinating neuropathy.[169]

The neuromuscular symptoms of diphtheria are often transient and directly proportional to the interval of time between initial infection and onset of symptoms.[167] Over 70% of patients recover fully from this disease, while mortality is approximately 3%.[168] Treatment of acute severe diphtheria infection includes the use of diphtheria antitoxin, antibiotics, and supportive respiratory care.

Diphtheria antitoxin is developed from horse serum for use in acute diphtheria infections. The antitoxin can produce serious adverse reactions that include: anaphylaxis, a rapid rise in body temperature within 20–60 minutes of injection, and serum sickness that develops more gradually during the first 14 days after administration of antitoxin. A predose conjunctival or intracutaneous test with diluted antitoxin is recommended. Some have recommended premedication with 0.3 mL of epinephrine hydrochloride solution (1:1000). Regardless of pretreatment, it is essential that 1.0 mL of epinephrine hydrochloride (1:1000) and diphenhydramine be made available prior to administration of antitoxinin in case of an immediate hypersensitivity reaction.[167] The amount of antitoxin given is determined by both the severity of the disease and the primary site of infection with effectiveness based on early administration.[170] Antitoxin is given intravenously in saline over 60 minutes with a 10% chance of serum sickness.[167]

Antibiotics are also effective in treating diphtheria. Their judicious use eradicates *c. diphtheriae*, preventing local spread and transmission to other contacts. Penicillin, erythromycin, Rifampin, or a combination of these medications have been utilized effectively.[167]

As with poliomyelitis, prevention is paramount in reducing both mortality and morbidity from this disease.

Representative Preventative Vaccines

Poliomyelitis vaccine

The vaccine for polio comes in oral (OPV; Sabin) and injectable inactive (IPV; Salk) preparations. The use of the polio vaccination has been effective in reducing the incidence

of poliomyelitis from 350,000 reported cases in 1988 to 1919 reported cases in 2002.[165] Over this same period of time the number of countries with poliomyelitis cases has dropped from 125 to 7.[165] The benefits of the OPV form are its cheaper cost, ease of administration, and spread to nonvaccinated contacts.[171] OPV is more effective in assuring whole body resistance to infection and is the treatment of choice to control large outbreaks of polio. There are, however, very low risks of creating paralysis in individuals receiving OPV. OPV uses three attenuated strains of the virus that may replicate, mutate, and be excreted from the human intestine in the form of a vaccine derived polioviruses (VDPVs).[172] Vaccine derived polioviruses have the potential to spread and mutate through nonimmunized persons and ultimately cause a vaccine associated paralytic poliomyelitis (VAPP). From the period of 1961 to 1989, the United States averaged nine cases a year of VAPP.[173] Because the frequency of naturally occurring cases of polio is virtually zero for the United States and because of the risk of VDPVs causing paralysis, in 2000 IPV was adopted as the exclusive vaccination for poliomyelitis in the United States.[173]

OPV vaccination is contraindicated in pregnancy, or if a patient or household contact has HIV or another immunodeficiency state.[174] IPV is also contraindicated in a pregnant woman and may cause an anaphylactic reaction four hours post injection.[174]

Diphtheria vaccine

The vaccine for diphtheria can be given with the tetanus vaccination, or with the tetanus and pertussis vaccination in the diphtheria-tetanus-(acellular) pertussis (DTaP) preparation. The diphtheria portion of this vaccination is produced from the diphtheria toxoid. Given as an intramuscular injection, this vaccine has dramatically decreased the rate of diphtheria from 97,774 cases in 1980 to 9,864 cases in 2004.[175] Even patients who develop diphtheria should receive the vaccination since immunity is not guaranteed as a result of a prior exposure.[168] Side effects from the vaccination include anaphylaxis, an increased rate of febrile seizures on the day of vaccination, fever, prolonged crying, and hypotonic-hyporesponsive episodes.[176]

Toxin reducing agents

The peripheral nervous system is particularly susceptible to axonal injury by environmental and/or naturally occurring toxins. Toxic exposures may occur through accidental or purposeful ingestion, overuse of prescribed medication, or through in vivo production by an infectious agent. At high dosages, nearly every prescribed substance has the potential to produce a toxic effect on the body. Following are three examples of prevalent toxicities in neuromuscular medicine and their corresponding therapies.

Representative Diseases That Use Toxin Reducing Agents

Lead toxicity (plumbism)

Lead toxicity is the symptomatic overexposure to the element lead. This toxicity is categorized into either acute or chronic exposure. Acute exposures are most commonly seen in the pediatric population due to ingestion and present with abdominal pain, ataxia, lethargy, pica, and anemia.[177,178] Chronic exposure to lead may present more insidiously with irritability, anorexia, insomnia, gingival-tooth demarcation (lead-lines), myalgias, abdominal cramping, hypertension, nephropathy, headache, gout, memory loss, microcytic anemia, choreaform movements and persistent cognitive dysfunction.[177,178] Neurological symptoms of chronic lead intoxication include encephalopathy, seizure, tremor, headache, peripheral neuropathy, weight loss, hand extensor paralysis and mononeuritis multiplex.[177,178] Peripheral neuropathies caused by chronic lead exposure typically present with distal upper extremity weakness, atrophy, and lost reflexes.[178] On electrodiagnostic testing there are signs of sensory and motor axonal damage along with demyelinating features; and, motor symptoms usually predominate over sensory symptoms.[178]

Work up of suspected lead toxicity should include a careful inquiry about exposure, occupational hazards, and moonshine use (the apparatus used to produce this beverage often has lead components). If acute intoxication is suspected, both urine and serum lead levels should be checked. The work up for chronic lead exposure includes: measurements of free erythrocyte protoporphyrin (FEP) and zinc protoporphyrin (ZZP), an x-ray fluorescence test (to determine the lead burden in the bone), an ethylenediaminetetraacetic acid (EDTA) lead mobilization test, and the determination of the ratio of aminolevulinate acid dehydratase (ALAD) to restored ALAD.[177,179,180]

Treatment of both acute and chronic lead toxicity consists of removal of environmental and occupational sources as well as chelation therapy. Chelating agents are numerous and include: calcium disodium versenate (edetate disodium calcium), British antilewisite (BAL) in oil (dimercaprol), cuprimine (d-penicillamine), and chemet (succimer).

In one trial of patients with chronic lead exposure and subsequent kidney disease, two months of chelation therapy with calcium disodium EDTA (1 g/week) showed substantial benefit through a reduced progression of renal disease.[181]

Secondary symptoms of lead toxicity also require treatment. If seizures occur, a benzodiazepine or antiepileptic medication should be utilized. Additionally, if brain edema occurs, as is common in severe lead encephalopathies, treatment may be implemented with hyperventilation, and/or osmotic agents.[178]

Prognosis depends on coexisting conditions and the extent of exposure. Recovery of motor deficits should be expected in all but the most severe cases.[178]

Thallium toxicity

Thallium is an odorless and tasteless heavy metal used commonly in industry.[182,183] Thallium toxicity occurs most commonly through ingestion, although exposure can occur through dust inhalation, dermal absorption through gloves, and though accidental snorting of what was thought to be cocaine.[184] Exposure to an 8–15 mg/kg dose is often lethal within 10 days.[183] Proposed mechanisms of toxicity include disruption of mitochondrial sulphydryl groups, and interference in riboflavin homeostasis.[184,185] Gastrointestinal features are present within 48 hours of exposure and may include nausea, vomiting, diarrhea, unresponsive constipation, gastritis, paralytic ileus, parotid and pancreatic damage. Neurological features of toxicity occur within two to five days and can include symmetric distal extremity hyperesthesia, paraesthesias, headaches, ptosis, strabismus, optic neuropathy/ atrophy, myalgia, myopathy, acute motor neuropathy, autonomic neuropathy, dementia, coma, chorea, ataxia, cranial neuropathies, delirium and psychosis.[184,178,182] A peripheral polyneuropathy can occur that involves distal axonal loss with secondary demyelination and small unmyelinated fiber involvement.[178,182] In a study of one patient who had thallium intoxication it was found that an axonal neuropathy at the distal plantar nerves developed before sural or peroneal involvement, with some normalization of electrodiagnostic testing at two years.[183]

Polyneuropathies secondary to low dose thallium ingestion begin with sensory complaints that develop days after the initial exposure.[178] Later effects of toxicity include cardiac arrhythmias, a pigmented band of scalp hair, disrupted pacemaker function, hyperkeratosis, Mee's lines and the classically stated tractional alopecia two weeks post exposure.[184,182,183]

Diagnosis depends on clinical history and thallium levels, which may be tested in blood, urine, or tissue.[178] If clinical suspicion of thallium toxicity is high, and initial blood levels are normal, a potassium chloride challenge may release abnormally high sequested body thallium stores into the urine for diagnosis.[178] Electrodiagnostic studies in thallium toxicity may show slowing of motor conduction velocities, reduction of sensory nerve amplitude potentials, and evidence of motor axonal degeneration.[178]

Treatment consists of Berlin blue. If ingestion is within 48 hours, charcoal use and hemodialysis may also be beneficial.[184] In contrast to their benefit in excess accumulation of lead, dimercaprol, EDTA, penicillamine, and dithiocarbamate are not effective treatments in thallium toxicity and dithiocarbamate can exacerbate encephalopathy.[184] Paralytic ileus is a common feature of thallium toxicity, and the addition of mannitol to Berlin blue increases effectiveness of treatment. Contractures and stomatitis may also occur with thallium toxicity, with benefit obtained with physical therapy and periodic mouth washes.[184]

The prognosis after thallium toxicity depends on the amount of exposure. Severe intoxication may lead to residual sensory loss and CNS dysfunction. In mild cases, hair growth may begin after 10 weeks and recovery from motor and sensory symptoms may occur fully after six months.[178]

Botulism

See the previous section on representative diseases that benefit from medication affecting the neuromuscular junction for clinical information about botulism.

Representative Toxin Reducing Agents

Lead chelating agents

The treatments for plumbism include: calcium disodium versenate (edetate disodium calcium, CaEDTA), British antilewisite (BAL) in oil (dimercaprol), cuprimine (d-penicillamine), and chemet (succimer). Each of these treatments have a separate side effect profile. Of these, succimer and penicillamine may be used for milder cases, while both CaEDTA and BAL can be used in combination for the more severe intoxications.[178]

Botulism immune globulin (big)

Human botulism immune globulin was approved for use in infant botulism by the FDA in October 2003.[86] Equine botulinal antitoxin exists, but is not recommended for infant botulism.[89] Adults receiving the equine antitoxin should be tested for hypersensitivity to equine sera before administration.[94] Side effects of BIG vary, but may include hypertension, irritability, contact dermatitis, gastrointestinal symptoms, or atelectasis.[186]

Botulism trivalent antitoxin

Botulism trivalent antitoxin containing antibodies against A, B, and E toxins may be used intravenously for postexposure prophylaxis against botulism. When given in a timely fashion it minimizes the progression of nerve damage although it does not reverse the paralysis.[90,87] The antitoxin works through binding the free toxin molecules before they become attached to the nerve endings.[88] If a non-A, B, or E botulism toxin is suspected, an investigational heptavalent (ABCDEFG) antitoxin exists through the U.S. Army.[87]

Hypersensitivity reactions such as urticaria and serum sickness, may occur in response to antitoxin therapy.[87] To search for a potential hypersensitivity, a challenge dose may be given before full administration of the pharmacologic treatment is administered. In addition, diphenhydramine and epinephrine should be available as noted previously for treatment of anaphylaxis.[87]

An investigational prophylactic pentavalent (ABCDE) botulinum toxoid, which works through a passive immunity process, is currently available for military personnel and at-risk laboratory workers.[87,187]

Berlin blue

The antidote for thallium toxicity is Berlin (formerly Prussian) blue or potassium ferric hexacyanoferrate (II).[184] Berlin blue combines with thallium ions in the intestinal lumen forming insoluble complexes while increasing fecal excretion.[184] This process may reduce the elimination half-life of thallium from eight to three days.[184]

Channelopathy altering agents

The channelopathies are a relatively underdiagnosed and understudied group of disorders that received increased attention over the past several decades. Cures are not available for these diseases. However, agents that improve the physiologic alterations of the malfunctioning channels have been identified, and they have the potential to provide substantial symptomatic benefit. Currently, therapeutic agents are in use to alter the concentrations of serum electrolytes, including potassium supplementation, selective diuretics, and beta-adrenergic agonists, as well as medications that reduce clinical myotonia. All these pharmacological approaches have found a therapeutic role in the management of patients with specific channelopathies.

Representative Diseases That Use Channelopathy Altering Agents

Hypokalemic periodic paralysis

Hypokalemic periodic paralysis (HypoPP) type-1 is an autosomal dominant disorder associated with mutations of the alpha subunit of the voltage-sensitive muscle calcium channel gene on chromosome 1q.[188] HypoPP type-2 is a disease with similar clinical features that is caused by a mutation on the alpha-subunit of the sodium channel gene on chromosome 17q.[188] Clinically, patients with HypoPP have episodic generalized or focal weakness associated with carbohydrate ingestion, alcohol use, emotional stress, morning arousals, and rest (usually with food intake) after exercise.[188] These episodes typically begin in childhood or early adulthood and may last from hours to days.[188] Serum potassium levels may reach the 2–3 mmol/Liter range during attacks, placing patients at risk for a cardiac arrhythmia. The pathophysiologic features of HypoPP include reduced membrane excitability, depolarization secondary to hypokalemia, insulin potentiated depolarization, and episodic hypokalemia.[188] The exact process(es) that initiate and terminate the spontaneous attacks of weakness and paralysis is unclear, but may be related to reduced surface membrane excitability and the inactivation of sodium channels.[188]

The diagnosis of HypoPP is based on clinical features, electrodiagnostic findings, hypokalemia during attacks, and genetic testing when it is available and positive. Cases with atypical clinical presentations and equivocal laboratory findings remain a challenge to diagnosis because of the relative unavailability of DNA testing for known mutations and because of the existence of kindreds having a typical clinical profile for HypoPP and no specific mutation in the calcium channel or sodium channel genes noted previously. Electrodiagnostic features of the disorder include normal baseline compound motor and sensory nerve action potentials with a reduction in the amplitudes of the evoked compound muscle action potential during attacks of weakness. Electromyography in HypoPP does not show myotonia; however, a reduction in the size and number of motor unit action potentials may occur during clinical attacks.[188] Repetitive stimulation evaluation using the long exercise test may reveal an immediate increase in CMAP amplitude followed by a progressive drop of 50% over 20–40 minutes.[188] Laboratory investigations typically show a low serum potassium concentration during episodes of weakness, and an elevated level of creatine kinase may also be present. Muscle biopsy may show no alteration or have vacuoles with signs of muscle tissue necrosis and degeneration.[188] Some patients in the later stages of the disease develop fixed muscle weakness that may result from the cumulative effect of subclinical attacks of weakness and a lack of longterm continuation of preventive treatment.

Treatment consists of adjusting the patient's lifestyle to avoid triggering factors and the use of preventive medications such as carbonic anhydrase inhibitors, potassium-sparring diuretics, and potassium supplementation. Potassium supplementation is used as a prophylactic and abortive therapy. Acute attacks can be treated with an initial oral dose of potassium (0.25 meq/kg) followed by a second smaller dose at 30 minutes if symptoms persist.[188] In addition, daily supplementation can be used to maintain baseline potassium levels. The authors prefer to use capsulated forms of potassium chloride for daily maintenance while utilizing liquid preparations for acute attacks due to its quicker absorption time and greater tolerability in patients with bulbar symptoms. Electrolyte and electrocardiographic monitoring with frequent assessment of blood pressure during attacks is imperative given the possibility of cardiac arrhythmias.

Hyperkalemic periodic paralysis (hyperpp)

Hyperkalemic periodic paralysis is an autosomal dominant disorder with nearly complete penetrance caused by mutations in the alphasubunit of the human skeletal muscle voltagegated sodium channel gene on chromosome 17q23.[188] Symptoms typically begin in early childhood with morning attacks of paralysis and hyporeflexia lasting minutes to hours.[188] Weakness is usually generalized and tends to spare the facial and respiratory muscles, but occasionally may be focal restricted to one limb or one side of the

body. Attacks are precipitated by rest after exercise, fasting, stress, cold, or potassium supplementation.[188] Much remains to be learned about the initiating and recovery mechanisms of the attacks of weakness and the associated changes in serum potassium in patients with HyperPP; however, it is thought that the mutations responsible for HyperPP cause the slow inactivation of the sodium channel to be inhibited, producing a persistent sodium current and subsequent paralysis.[188]

Diagnosis is based on clinical features, electrodiagnostic testing, provocative exercise testing, and DNA analysis when it is available and is positive. Like HypoPP, in HyperPP, the amplitude of the evoked compound muscle action potential declines during acute attacks of weakness. Serum potassium levels are often elevated and occasionally there is a mild elevation of creatine kinase.[188] Electromyographic investigations may be normal, or show myopathic motor unit action potentials, or demonstrate a reduction in the size and recruitment of motor unit action potentials in weak muscles.[188] Unlike HypoPP, in HyperPP myotonia on needle electromyographic study may occur prominently during an attack of weakness.[188] Clinical myotonia may also be present and show a warm-up response with improvement after repeated muscle contractions. Electrodiagnostic evaluation in patients with HyperPP using repetitive stimulation after a period of brief exercise may demonstrate an immediate increase in the amplitude of the compound muscle action potential amplitude followed by a progressive 50% decline in the amplitude of the compound muscle action potential over a 20–40 minute period.[188] If the diagnosis of HyperPP is in doubt, it is reasonable to request DNA testing. However, as noted for the other channelopathies, there is a limited availability of DNA mutation testing and the testing that is available for clinical screening does not search for all the mutations known to cause HyperPP.

The principle treatment for HyperPP is preventive. Thiazide diuretics and carbonic anhydrase inhibitors are used. Reduction of the severity and frequency of attacks can be obtained though the use of acetazolamide.[188] Dosages of acetazolamide may range from 125 mg orally twice a day up to 250 mg four times a day with some cases of refractory disease requiring 1500 mg a day for perceived benefit.[188] Alternatively, dichlorphenamide can be used at 25 mg twice a day up to 50 mg three times a day.[189] If during an acute attack of weakness the patient has severe hyperkalemia, intravenous glucose administration and insulin may be necessary to reduce serum potassium levels. During severe attacks of weakness in HyperPP, as is the case in severe attacks of HypoPP, it is important to monitor vital signs, the electrocardiogram, and serum electrolytes. Some patients change their lifestyle to prevent episodic weakness. They will consume frequent low-potassium carbohydrate meals, avoid strenuous activity followed by rest, and will take beta-adrenergic agonists to stave off an impending attack.[190] These additional preventive measures are much less effective than thiazide and carbonic anhydrase inhibitor treatment, and often lead to obesity.

Andersen-tawil syndrome (ats)

Andersen-Tawil syndrome (ATS) is an autosomal dominant periodic paralysis characterized by episodes of generalized weakness in patients with dysmorphic facial features, prolongation of the QT interval and ventricular arrhythmias. The dysmorphic features of ATS may include shortness, a high arched palate, low-set ears, a broad nose, micrognathia, hypertelorism, clinodactyly, a short index finger, and syndactyly of the toes.[188] Patients may have only some of these dysmorphic features and may have only infrequent, mild attacks of weakness. The typical episodes of weakness may be triggered by rest after exercise or alcohol consumption.[188] Some patients may have muscle aches, potassium imbalance (high, low, or normal), or prominent U waves on electrocardiogram (EKG).[188] Some patients may have fixed weakness, especially of proximal shoulder girdle, facial, and neck flexor muscles. The etiology of ATS is thought to be secondary to mutations of the inward rectifier potassium channel gene *KCNJ2*, which encodes the inward rectifier potassium channel Kir2.1 protein.[191] The exact process that leads to the episodic weakness is unknown, but may be related to reduced pip2-related channel activation and altered interactions with actinbinding filamin.[188,191,192]

Nerve conductions studies are normal in ATS, although the long form of repetitive stimulation-exercise testing, similar to the other hereditary types of periodic paralysis, produces an immediate increase in the amplitude of the evoked compound muscle action potential followed by a progressive decline of approximately 45% after 20–30 minutes.[188] Unlike HyperPP, no myotonia is found on needle electromyographic investigation. Muscle biopsy may show tubular aggregates. DNA analysis for certain mutations is now obtainable through certain research centers. However, it is important to note that some kindreds with ATS have not yet had the causative mutation identified, and that DNA testing is primarily helpful in confirming the diagnosis only if it is positive.

Treatment consists of the carbonic anhydrase inhibitors acetazolamide and dichlorphenamide, which may limit episodes of periodic weakness.[188] Additionally, cardiac evaluation is imperative in this population given the frequency of cardiac arrhythmias and EKG abnormalities. Management of the arrhythmias is often a challenge and requires serial monitoring by cardiology consultants.

Paramyotonia congenita (pc)

Paramyotonia congenita is an autosomal dominant disorder caused by mutations of the alphasubunit of the voltage-gated sodium channel gene on chromosome 17q23.[188] Clinically, PC has episodes of painless muscle stiffness provoked by cold and prolonged exercise with both clinical and electrical myotonia. Symptoms typically begin in early childhood, with early involvement of the bulbofacial, neck, and hand muscles.[188] Stiffness, especially in the eye muscles and forearm muscles, increases with repeated contractions. Repeated muscle contractions of the facial and hand muscles after cold exposure frequently causes flaccid weakness that may require several hours to resolve. Variants of PC may resemble HyperPP. These patients have typical paradoxical myotonia of facial and forearm muscles, as well as flaccid muscle weakness with exercise following cold exposure; but, in addition, the patients with this variant of PC have periodic attacks of weakness typical for those in HyperPP that are unprovoked by exercise following exposure to cold.[188]

Electrodiagnostic testing typically shows diffuse myotonic discharges that tend to predominate in the distal muscles.[188] After cooling of their muscle in water, fibrillation potentials develop. After the muscle temperature falls below 28°C, the fibrillation potentials disappear. At temperatures less than 20°C, an electrically silent contracture and paralysis develops and the myotonic discharges disappear entirely.[188] The short repetitive stimulation-exercise test is useful in paramyotonia congenita. After exercise and cold exposure there is a decline in the amplitude of the compound muscle action potential and there is a marked delay in recovery to return to their baseline amplitude.[188]

Treatment of PC is preventive. Avoidance of cold temperatures, especially in association with repeated muscle contractions, is usually effective. However, affected individuals who need to exercise in cold environments usually choose to take medications that prevent stiffness and flaccid weakness following cold exposure. The class 1b antiarrhythmic drugs, mexiletine and tocainide, prevent both the paradoxical stiffness and flaccid weakness with exercise following exposure to cold. Tocainide is not available for use in many countries because of toxic side effects on the bone marrow.[188]

Mexiletine is widely available and is often effective at starting dosages of 150 mg twice daily.[188,193] If spontaneous attacks of periodic weakness (not-stiffness) occur in a patient who also has typical symptoms of PC, treatment with a thiazide antidiuretic, such as hydrochlorothiazide, is helpful in preventing episodes of spontaneous weakness.[188] Acetazolamide has also been useful in preventing attacks of spontaneous weakness in patients with this variant type of PC; however, worsening of weakness has been observed in certain patients with markedly temperature sensitive PC.[188] For this reason the combination of mexiletine and diuretic therapy is the preferred initial treatment for the variant form of PC with HyperPP like symptoms. Mexiletine alone is the initial treatment for classical PC.

Representative Channelopathy Altering Agents

Carbonic anhydrase inhibitors: acetazolamide and dichlorphenamide

Carbonic anhydrase inhibitors are the treatment of choice for weakness in HypoPP, and an alternative treatment option for weakness in HyperPP.[194] The mechanism of action of carbonic anhydrase inhibitors in hyperkalemic periodic paralysis is not entirely clear, but it has been hypothesized to be secondary in part to their potassium lowering effect. This rationale does not explain the benefits seen in HypoPP. Another hypothesized mechanism underlying the beneficial effect of carbonic anhydrase inhibitors stems from the mild acidosis and increased Ca^{2+}-activated K^{+} channel activity that occurs during the use of this class of medication.[192]

Side effects of carbonic anhydrase inhibitors include: nausea, anorexia, paraesthesias, depression, mood instability, sleepiness, confusion, rash, alteration in the taste of

carbonated beverages, reduced cell count, vision alteration, and nephrolithiasis.[192] Serial measurement of liver function and complete blood counts is necessary with use of these medications.

Compared to acetazolamide, dichlorphenamide is a more potent carbonic anhydrase inhibitor. The use of dichlorphenamide has gained popularity for patients refractory to acetazolamide. Dichlorphenamide may cause less metabolic acidosis and nephrolithiasis compared to acetazolamide although confusion is not an uncommon side effect with its use.[188,194] In a double-blind, placebo-controlled trial, dichlorphenamide was found to reduce the attack severity and frequency in HypoPP, while reducing attack rates in potassium sensitive periodic paralysis.[189] Further studies, including a direct comparison of acetazolamide to dichlorphenamide, need to be completed to ultimately confirm its efficacy.

Thiazide diuretics

Thiazide diuretics, specifically hydrochlorothiazide (HCTZ), are a mainstay of treatment in hyperkalemic periodic paralysis and may also improve symptoms in paramyotonia congenita. Potential side effects of hydrochlorothiazide include allergic reaction, weight loss, nausea, headaches, confusion, dizziness, thrombocytopenia, and hypotension.[192]

Potassium chloride

This medication is used as maintenance and abortive therapy in hypokalemic periodic paralysis. Tablets and liquid preparations are available as well as intravenous solutions. Intravenous administration of potassium can exacerbate hypokalemia if given with glucose, or can cause acute hyperkalemia if given with saline without careful monitoring.[188] Hyperkalemia is a potential side effect of potassium chloride supplementation and frequent monitoring of serum electrolytes and the electrocardiogram is necessary to establish a safe and stable maintenance dosage. Hyperkalemia can produce cardiac arrhythmias and/or severe muscle weakness.

Class 1b antiarrhythmic medications: mexiletine and tocainide

As noted previously, mexiletine and tocainide are lidocaine derivatives and class 1b antiar-rhythmics. They bind to the sodium channel, affect late sodium current, and stabilize the muscle membrane potential. Mexiletine is an effective treatment in paramyotonia congenita, myotonic dystrophy, and potassium-aggravated myotonias. Tocainide is also effective, but it is not available in many countries due to its undesirable side effects. Common side effects for mexiletine include gastrointestinal distress, lightheadedness, tremor, and rash, but they usually do not prevent its continued use following a taper in dosage.[188] Prior to initiating treatment with mexiletine it is necessary to obtain baseline blood count, serum electrolytes and liver function studies as well as an electrocardiogram. Repeated blood counts, liver function studies, and electrocardiograms are recommended at three month intervals for the first six months of treatment and at six month intervals thereafter.

Antimicrobial agents

An infectious etiology of neuromuscular disease should not be overlooked given the availability of effective antimicrobial therapies. Diseases such as leprosy and syphilis are declining in incidence, but remain solid examples of how systemic infection can produce focal neuromuscular disease. Likewise, Lyme disease is a more recently described disease that through timely therapy can have its clinical effects limited.

Representative Diseases That Use Antimicrobial Agents

Leprosy

Leprosy is a chronic infection caused by the acid-fast, gram-positive bacillus mycobacterium leprae that has dramatic effects on the skin and peripheral nervous system. Leprosy induces clinical symptoms by altering immune regulation and cellular immunity.[195]

The classifications of leprosy include four different forms: tuberculoid, lepromatous, borderline, and indeterminate. High levels of cytokines, including interleukin-2 and gamma interferons, are found in tuberculoid leprosy, whereas elevated IL-4 and IL-10 levels are found more predominantly in lepromatous leprosy.[195]

Tuberculoid (paucibacillary) type leprosy presents with 1–2 erythematous or hypopigmented anesthetic macules with sensorimotor axonal loss in the distribution of the lesions. Tuberculoid leprosy can also cause enlargement of single peripheral nerves. Lepromatous (multibacillary) type leprosy is a cell-mediated immune process that may disseminate hematogenously producing widespread erythematous lesions, sensory and motor nerve axonal loss, hypoesthesia over the extensor surfaces, ears, and legs, loss of facial hair, dysarthria, and diffuse weakness over the distal intrinsic muscles. Borderline type leprosy presents with multiple tuberculoid type lesions, asymmetric widespread sensory and motor nerve axonal loss, and anesthetic peripheral nerve lesions. Indeterminate type leprosy presents with small hypopigmented macules with or without sensory symptoms.[195,196,197]

The diagnosis of leprosy is based on clinical history and supported by a positive lepromin skin test, a positive skin biopsy showing granulomas and m. lepra bacilli, a positive nerve biopsy, and electrodiagnostic studies demonstrating axonal degeneration, focal demyelination and denervation.[195]

Pharmacologic treatment consists of eradication of the gram positive bacilli, and prevention of sensitivity reactions to treatment. Specific regimens have been developed based on the type of leprosy infection; although controversy still exists regarding the duration required for cure. In paucibacillary leprosy, a six month treatment with rifampin and dapsone is utilized.[197] For multibacillary leprosy, a one to two year treatment of rifampin, dapsone, and clofazimine is used (with the duration of treatment often debated).[197] Lastly, for single lesion paucibacillary leprosy, one dose of rifampin, ofloxacin, or minocycline may be given with effective results.[197] Despite appropriate treatment, peripheral nerve damage may progress. If this occurs, a course of prednisone with a taper over five months may be beneficial in halting the progression of disease.

Treatment of leprosy is often complicated by relapse. An inflammatory response to mycobacterium eradication often occurs and is known as a *reversal reaction*. This reaction may cause a painful neuritis or swelling of preexisting skin lesions. Treatment with steroids, clofazimine, or thalidomide may be beneficial in reversal reactions.[197]

Erythema nodosum leprosum with new subcutaneous nodules may also develop after six months of treatment. This reaction may be treated with the immunomodulating medication thalidomide.[197]

Lyme disease

Lyme disease, caused by the gram-negative spirochete borrelia burgdorferi, is the most common tic born disease in North America.[198] Acute infections may cause erythema migrans (an erythemic expanding, target shaped focal rash), fatigue, headache, mild stiff neck, joint and muscle aches, and fever, while disseminated disease may later cause chronic cardiac, arthritic, and neurological manifestations.[198,199] Neuromuscular symptoms include seventh cranial nerve palsies, motor and sensory neuropathies, mononeuritis multiplex, plexopathies, entrapment neuropathies, and cerebellar ataxia.[200]

Electrodiagnostic studies in Lyme disease show proximal and distal axonal loss, reduced sensory conduction velocities and/or active denervation in the paraspinal, girdle, and distal limb muscles.[201] In chronic cases, motor conduction velocities may be reduced with prolonged F-wave responses suggestive of a secondary demyelinating process.[201]

The exact pathogenesis of Lyme disease remains undetermined. Possible mechanisms include a direct tissue infection, autoantibody action on nerve proteins, and tissue destruction through B-cell induced cytokine action.[195]

There are multiple ways to test for Lyme disease. These methods include: microbial isolation from an erythema migrans rash, serologic testing with enzyme-linked

immunological assays and western blot testing, indirect immunofluorescence assays, T-cell proliferative assays, polymerase chain reaction testing, and urinary antigen detection. According to an evidencebased review, sequential testing with enzyme-linked immunosorbent assay and western blot is the most effective method of ruling in or ruling out Lyme disease when the clinically based pretest probability is 0.2 to 0.8.[198]

Treatment recommendations are based on presenting symptoms. In adult patients presenting with only erythema migrans or erythema migrans with an uncomplicated facial nerve palsy, 100 mg of doxycycline given by mouth twice a day for 10–21 days, amoxicillin 500 mg three times a day for 14–21 days, or cefuroxime 500 mg twice a day for 14–21 days are different treatment options.[202] Doxycycline may be the preferred agent given the preponderance of clinical data regarding its use in Lyme disease and its concordant use as a treatment in human granulocytic anaplasmosis, which is also a disease spread by an ixodestick.[202]

In adult Lyme disease patients who develop heart block or meningismus, treatment with intravenous ceftriaxone at 2 g/day is recommended.[202] Alternatively, cefotaxime may be used. Complications of antimicrobial treatment include an increase in systemic symptoms and the size of the preexisting skin condition.[199] In Lyme cases in which there is severe pain, corticosteroids may provide relief.[203]

For prophylaxis after a tick bite, a single dose of doxycycline at 200 mg can prevent disease. For primary prevention in high-risk patients, a lipidated recombinant OspA protein vaccine may prove effective. Its use is limited given the controversy regarding its efficacy and reported side effects.[201]

The prognosis for antibiotic treated Lyme disease is good when cardiac symptoms do not predominate; however, 10% of patients have persistent fatigue or pain secondary to the disease five years after treatment.[202] In most patients, radicular pain symptoms abate at two to 16 weeks, with improvement of Lyme induced peripheral neuropathies seen after appropriate antibiotic treatment.[195,203]

Representative Antimicrobial Agents

Dapsone

Dapsone is a bacteriostatic, folate antagonist utilized for paucibacillary leprosy, multibacillary leprosy, dermatitis herpetiformis, and other infectious processes. Possible side effects include a severe hemolytic anemia in G6PD deficiency, exfoliative dermatitis, and occasionally a dose induced peripheral neuropathy.[204]

Rifampin

Rifampin is a bactericidal medication utilized for both paucibacillary and multibacillary leprosy. It is typically given in 600 mg doses once a month under supervision. There is limited resistance to this medication. Side effects such as urine discoloration, headache, rash, gastrointestinal symptoms, liver dysfunction, fever and mouth ulcerations may occur.[205]

Clofazimine

Clofazimine is a bacteriostatic medication in the nonsteroidal anti-inflammatory medication family and is used for multibacillary leprosy. Dosages of 300 mg once a month or 50 mg once a day are given. It may cause gastrointestinal discomfort or a skin rash, and should not be used in pregnancy.[206]

Minocycline

Minocycline is a bacteriostatic, protein synthesis inhibiting semisynthetic derivative of tetracycline used for single lesion paucibacillary leprosy among other infections. A single dose of 100 mg can be used for paucibacillary leprosy. Minocycline may cause dental staining, photosensitivity, gastrointestinal symptoms, renal toxicity, or hypersensitivity reactions and should not be given to the pregnant.[207]

Thalidomide

See Representative Immune Modulating Medications (page [link]).

Doxycycline

Doxycycline is a tetracycline derivative antibiotic utilized for syphilis, anthrax, Lyme disease (without advanced heart block or meningismus) and tic prophylaxis.[208] Photosensitivity reactions and pseudomembranous colitis may occur. This medication should not be used in pregnant or lactating women.[202] Gastrointestinal symptoms may be reduced if taken with increased quantities of fluid.

Amoxicillin

Amoxicillin is a broad spectrum bactericidal agent used for gram-positive and negative microorganisms.[209] This antibiotic can be used in noncomplicated cases of Lyme disease. Rash, diarrhea, hypersensitivity reactions, gastrointestinal symptoms, hepatic dysfunction, and pseudomembranous colitis may occur as side effects.[202,209]

Cefuroxime

Cefuroxime is a broad-spectrum cephalosporin antibiotic used for Lyme disease.[210] Like amoxicillin, rash, diarrhea, hypersensitivity reactions, hepatic dysfunction, and pseudomembranous colitis are possible side effects.[210] Other rare side effects of cefuroxime include seizure and angioedema.[210]

Ceftriaxone

Ceftriaxone is an intravenous broad-spectrum cephalosporin used for Lyme disease with secondary heart block and/or meningitis.[211] Rash, diarrhea, hypersensitivity reactions, pseudomembranous colitis, biliary lithiasis, or catheter infection may occur with use of this medication.[202,211]

Antimyotonic medications

Myotonia is a delay in the body's ability to relax following a voluntary muscle contraction, an external percussion of a muscle, or an electrical stimulation of a muscle's nerve supply. Myotonia is prominent in both dystrophic and nondystrophic myotonic disorders. It can also occur as a side effect of many medications and in certain endocrine disorders, such as, hypothyroidism. Myotonia causes decreased agility, slowed relaxation of grip, and stiffness of large limb and paraspinous muscles in myotonic dystrophy type 1 and 2, hyperkalemic periodic paralysis, paramyotonia congenita, potassium aggravated myotonia, and myotonia congenita. Often myotonia is noticed before weakness in the dystrophic forms of myotonia. Fortunately, effective symptomatic therapies exist for this life altering symptom.

Representative Disease That Uses Antimyotonic Medication

Myotonic dystrophy type 1 (dm1)

Myotonic dystrophy type 1 is a dominantly inherited, trinucleotide repeat, multisystem disease characterized by the triad of myotonia, weakness, and cataracts before the age of 50.[212] Other clinical manifestation may include: balding, temporal wasting, heart block, daytime sleepiness, hypersomnia, irritable bowel syndrome, dysarthria, and distal weakness that is greatest in the long finger flexors, intrinsic hand muscles, and foot dorsiflexors.[212] In the newborn, myotonic dystrophy may present with hypotonia, feeding difficulties, and respiratory failure.[212]

Myotonic dystrophy type-1 results from an unstable cytosine-thymine-guanine (CTG) trinucleotide repeat expansion on the 3' noncoding region of the gene for a serine and threonine kinase (myotonic dystrophy type-1 protein kinase, DMPK) on chromosome 19q13.3.[213–215] Different theories exist regarding the exact mechanisms by which the unstable trinucleotide repeat expansion produces the various clinical manifestations of DM1. One likely mechanism that underlies the muscle dysfunction in DM1 relates to a sequestration of the double-stranded RNA binding, nuclear regulatory protein, muscleblind, due to its abnormal binding to the abnormally expanded mutant mRNA that accumulates in the nuclei of cells in DM1.[212,216,217]

Diagnosis of DM1 isusually obtained through clinical history and findings, but the gold standard for diagnosis is the demonstration of abnormal expansion of CTG repeats (> 50 repeats) at the 19q13.3 locus for the DM1 gene.

Myotonic dystrophy type-1 is a multisystem disease. Health care providers in neurology, physical therapy, occupational therapy, orthopedics, ophthalmology, pulmonology, and cardiology are often involved in the care of the different manifestations caused by this disorder.[212] Devices such as orthotics and ambulatory assist devices may help with muscle function. Placement of a pacemaker may be life saving for patients with heart block or certain other cardiac arrhythmias. Noninvasive nasal ventilation is also useful in patients with respiratory insufficiency and may lessen the severity of hypersomnia, which often requires treatment with methylphenidate or modafinil.

Myotonic dystrophy type-1 patients often have delayed relaxation of grip, varying slurring of their speech, and abnormal motility of intestinal and other smooth muscles. These manifestations all are signs of myotonia. There are a number of medications that have been tried as treatment of myotonia in DM1. It appears that mexiletine may be the most effective.

Mexiletine is favored by many experts in the field as an antimyotonic agent. Recent data presented in abstract form from a seven-week, randomized, double-blind, crossover trial of two groups of 30 DM1 patients indicated that mexiletine at 150 mg and 200 mg dosages given three times daily is well-tolerated, safe, and effective in treating their myotonia.[212,218] Tricyclic medications have also been used. In a double-blind crossover trial of 15 patients with myotonic dystrophy, it was found that 75 mg per day of clomipramine was more effective then placebo in alleviating grip myotonia.[219] Imipramine, another tricylcic medication, was shown in a double-blind crossover study of 12 adult myotonic dystrophy patients to reduce grip and percussion myotonia compared to placebo independently of change in depressive symptomatology.[220] Additionally, the medication taurine at dosages of 100–150 mg/kg reduced perceived myotonia and EMG relaxtion time in a series of nine patients with myotonic dystrophy.[221] With the exception of the mexiletine trial these investigations have unfortunately lacked the statistical power and standardized methodology to adequately quantitate the degree of myotonia in DM1.

Further research is necessary to determine which of the previous antimyotonia treatments are the most effective in DM1 patients.[222]

Antimyotonic Agents

Taurine

Taurine is a naturally occurring membrane stabilizing amino acid that may act to reduce myotonia by increasing membrane conduction of potassium and chloride while modulating the availability of calcium.[221] In general, taurine is well tolerated; however, a generalized amino aciduria may occur with supplementation of this agent.[221] More studies are necessary to establish the role of taurine as an antimyotonia agent.

Tricyclic antidepressants: imipramine and clomipramine

The exact mechanism by which tricyclic antidepressant medications reduce myotonic symptoms is not well elucidated. One hypothesis is that tricyclic medications act to inhibit beta-2 adrenoreceptor stimulation through the activation of the sodium potassium pump thus reducing muscle excitability.[220]

Imipramine is a tricyclic antidepressant that is used in panic disorders and occasionally as an antimyotonia therapy. In addition to its action on beta-2 adreonoreceptor stimulation, it may block reuptake of norepinephrine and serotonin and serve as a receptor antagonist for acetylcholine and histamine. Common side effects include sedation, hypotension, blurred vision, arrhythmias, tachycardia, palpitations, dry mouth, constipation, and decreased sweating.[223]

Clomipramine is a tertiary amine and serotonin reuptake inhibitor used for depression, obsessive-compulsive disorders and occasionally as an antimyotonic agent. Like imipramine, clomipramine also blocks norepinephrine reuptake and antagonizes acetylcholine and histamine. Side effects of clomipramine are similar to imipramine with additional problems with sexual dysfunction, fatigue, and weight gain.[223]

Mexiletine

See Representative Channelopathy Altering Agents (page [link]).

Duchenne muscular dystrophy (dmd) altering agents

Duchene muscular dystrophy is an X-linked recessive disorder that causes progressive wasting and weakness of proximal hip and shoulder girdle, anterior abdominal, and neck flexor muscles in childhood and extends to most limb muscles in the teens. Respiratory, cardiac, and smooth muscles are also affected and become symptomatic in the mid and late stages of the disease. Mutation in the gene for dystrophin at the Xp21 locus leads to a severe deficiency or complete loss of dystrophin in the target tissues of the disease. The absence of normal levels of dystrophin causes muscle necrosis, fibrosis, and ultimately a loss of function presumably through a lack of dystrophin's mechanical stabilization and its effects on signaling across the muscle plasma membrane.[224] Symptoms, such as, weakness of the neck flexor and anterior abdominal muscles develop before age five and patients do not run. Calf muscle hypertrophy is prominent. Some patients have learning disabilities and other cognitive problems. Lordosis and toe walking become more prominent before ambulation ceases. In later childhood, patients become confined to a wheelchair, and flexion contractures (ankles, knees, hips, elbows, and wrists) and scoliosis progress in severity. In the late stages gastrointestinal hypomotility becomes a problem along with respiratory insufficiency and cardiomyopathy. Death usually results from respiratory and/or cardiac failure, but respiratory infections and pulmonary emboli can also play a major role as a cause of death.[224–227]

The diagnosis of DMD is based on: an onset of proximal weakness of neck flexor, anterior abdominal, hip and shoulder girdle muscles before five years of age; a marked elevation of serum creatine kinase (>10 times normal); and, positive whole blood DNA testing for the mutation in the gene for dystrophin in the Xp21 region or demonstration of the absence of dystrophin in muscle biopsy.[224] Muscle biopsy in DMD patients may also reveal variation in fiber size, foci of necrosis, hyalinization, deposition of fat and connective tissue as well as an absence of dystrophin on immunostaining.[228]

With genetic testing, 65% of the mutations are secondary to large deletions of the dystrophin gene, with duplications accounting for 6% to 10% of the cases.[229] These mutations can be detected with Southern blot, multiplex PCR, or multiple ligation probe amplification (MLPA).[229] If genetic testing is not positive in clear clinical cases, DNA testing of all exons, flanking intronic sequences, and promoters should be done to detect the remaining 30%–35% of Duchenne mutations.[229] If genetic testing is still negative, a biopsy should be performed to look for the absence of dystrophin.

Treatment in DMD at present involves oral corticosteroid therapy to delay progression of muscle weakness; and, supportive care that includes: nonsurgical and surgical treatment, as necessary, for contractures and scoliosis; leg bracing; wheelchair and scooters; noninvasive nasal/oral (or tracheostomy mediated) ventilation; beta blocker and ACE inhibitor therapy for cardiomyopathy; and dietary/stool softener treatment to facilitate bowel motility and to meet nutritional needs. Some patients require a feeding gastrostomy to maintain adequate fluid and nutritional intake.

Curative treatment strategies are based on stimulating dystrophin production (including approaches to deliver dystrophin minigenes to affected tissues), inhibiting the inflammatory responses that occur in muscle, stabilizing the muscle membrane and improving muscle repair.[225]

A summary of the role of corticosteroid therapy in treatment of patients with DMD appears in a recent Practice Parameter published by a committee supported by the American Academy of Neurology and Child Neurology Society.[230] Some of the highlights are noted here. In 1989, the results of a landmark double-blind, randomized, prospective study were published by Mendell and colleagues demonstrating that DMD patients receiving prednisone at dosages of 1.5 and 0.75 mg/kg/day had better muscle strength and function compared to those receiving placebo after a six month course of treatment.[231] Side effects included weight gain, a cushingoid appearance, and excessive hair growth.[231] The optimal dose of prednisone is 0.75 mg/kg/day.[232] The exact mechanism of corticosteroid benefit in DMD is not known, but may relate to actions on the inflammatory cascade, stabilization of the muscle membrane, modulation of inflammatory mediators, stimulation of repair processes, modification of proteolysis and calcium handling, enhancement of myogenesis, and inhibition of apoptosis through up-regulation of utrophin.[225,233]

Another corticosteroid that shows beneficial effects in patients with DMD is deflazacort, an oxazolone derivative of prednisone. Deflazacort is not available in the United States but studies from other countries have indicated that 0.9 mg/kg/day of oral deflazacort produces similar beneficial effects on muscle strength and function compared to 0.75 mg/kg/day of prednisone. Other studies have shown a beneficial effect of deflazacort in attenuating the progression of scoliosis and improving cardiac function.[233] Some have speculated that deflazacort is equally effective to prednisone with less side effects, but studies are warranted to compare these two medications directly in a controlled trial.[225,234] Like prednisone, the exact mechanism underlying the beneficial effects of deflazacort in DMD is unknown, but it may be secondary to the suppression of cellular immunity, humoral immunity, and phagocytic cell action with subsequently reduced membrane fibrosis and improved membrane stability.[225]

Recent studies have also shown some limited improvement in strength with oxandrolone in DMD.[233] Oxandrolone, an anabolic steroid, may activate the transcription of genes involved in anabolic pathways, antagonize cortisol binding to glucocorticoid receptors, and decrease catabolic pathways.[233,235] In a six-month, randomized, double-blind, placebo-controlled study giving oxandrolone 0.1 mg/kg/day to boys with DMD, patients had mild increases in isolated muscle strength but no significant improvement in overall strength score or timed function testing occurred.[236] The mild beneficial effects of oxandrolone may result from an effect on myosin, but it is clear that corticosteroid treatment has a much more pronounced beneficial effect in DMD compared to oxandrolone.

In the setting of pursuing pilot studies of gene therapy in DMD, patients received cyclosporine. It is likely that cyclosporine (given at a dosage of 5 mg/kg/day) may increase muscle strength in DMD. This observation raises the possibility that immunosuppression is an effective therapy in DMD. However, previous studies comparing the immunosuppressive drug azathioprine to prednisone and placebo, showed no difference between placebo and azathioprine on the progressive loss of muscle strength over 12 months of treatment. More investigations are necessary to establish whether the beneficial effects of corticosteroids occurs in part by immunosuppressive actions or through one of their other actions.[70]

A potential novel pharmacologically therapy in DMD is the modulation of calpains, a cysteine protease, which is increased in DMD mouse models.[237] Leupeptin, a calpain inhibitor may provide benefit, but further evidence of its efficacy and feasibility as a treatment in humans needs to be established.[225] Other therapeutic agents that are being studied in DMD patients include creatine monohydrate, CoQ10, myostatin blocking agents, β_2-adrenergic agonists, TNF-alpha, IGF-1, aminoglycoside therapy and nitrous oxide, while methods such as virusbased gene transfer, stem cell therapy, and myoblast transplantation offer promise and are also under investigation.[225,233,224]

Representative Duchenne Muscular Dystrophy Altering Agents

Deflazacort

Deflazacort is an oxazolone derivative of prednisone utilized in patients with Duchene muscular dystrophy. In one clinical trial, patients receiving this medication had the following side effects after nine months of treatment: cushingoid appearance (28%), increased appetite (50%), increased body hair (28%), and irritability and hyperactivity (21%).[238,234] Patients receiving this medication should also have periodic ophthalmologic evaluations due to the increased possibility of developing cataracts.

Oxandrolone

Oxandrolone is an anabolic steroid used in DMD. Contraindications include preexisting carcinoma of the prostate or breast, pregnancy, nephrosis or hypercalcemia. Potential side effects include peliosis hepatis, hepatic cancer, cholestatic hepatitis, premature bone maturation and edema.

Corticosteroids

See Representative Immune Modulating Medications (page [link]).

Cyclosporine

See Representative Immune Modulating Medications (page [link]).

Diet supplements[12]

The idea that diet supplementation may augment one's quality of life saturates our modern society. The use of many agents is based on speculation or incidental report alone. In diseases with no cure, such as mitochondrial processes, ALS, and various myopathies, the limitation of existing therapies prompts experimental supplement use. When known side effects are few, physicians often allow or even encourage patients to use such agents. To date, some supplements have been shown to provide a benefit, while other agents remain untested.

Representative Diseases That Use Diet Supplements

Mitochondrial disorders

The mitochondrial disorders are a large group diseases that may cause neuromuscular dysfunction and often lead to premature disability and mortality.[239] In many of these diseases, affected mitochondria are not able to convert carbohydrate, lipid or protein into the useable energy source adenosine triphosphate.[240] Disorders termed *mitochondrial* are typically due to a malfunction of the mitochondrial respiratory chain. Malfunction of the mitochondrial respiratory chain may interfere with cellular metabolism and specifically with the oxidative phosphorylation process used in aerobic metabolism.[239] Primary mitochondrial disorders include: mitochondrial encephalomyelopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), maternally inherited diabetes and deafness (MIDD), neurogenic ataxia with retinitis pigmentosa (NARP), Leber hereditary optic neuropathy (LHON), chronic progressive external ophthalmoplegia (CPEO), Kearns-Sayre syndrome (KSS), Leigh syndrome, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), coenzyme Q10 (ubiquinone) deficiency, and Pearson syndrome. Organ system dysfunction is widespread in mitochondrial disease with the brain, peripheral nervous system, muscle, heart, and hormone-producing glands most affected due to their heavy dependence on mitochondria to produce energy.[239] Most abnormalities of mitochondrial DNA are transmitted from mother to child through the oocyte; however, some mitochondrial disorders such as

progressive external ophthalmoplegia, may have autosomal recessive or dominant forms.[241]

The clinical features of mitochondrial disease vary widely. In mitochondrial myopathies, proximal weakness, and reduced muscle bulk are common, although some patients may have normal muscle strength with activity-induced fatigue.[241] Other features of mitochondrial myopathies include sensory-neural hearing loss, diabetes, migraine headaches, short stature, or an insidious onset of ptosis and/or ophthalmoplegia.[241] Kerns-Sayre is known for the triad of ophthalmoplegia, pigmentary retinopathy, and age of onset before 20, although cardiac conduction block, cerebellar dysfunction, hearing loss, endocrinopathies, seizure, electrolyte imbalance or raised CSF protein may occur.[241] Myoclonic epilepsy with ragged-red fibers' clinical features include myoclonus, generalized epilepsy, ataxia, and ragged-red fibers on muscle biopsy. Hearing loss, dementia, exercise intolerance, lactic acidosis, and lipomas may also occur.[241] Mitochondrial encephalomyelopathy with lactic acidosis and stroke-like episodes has the cardinal features of strokelike episodes before age 40, seizure, dementia, and/or lactic acidosis.[241] Early development may be normal. Like other mitochondrial disorders MELAS patients may experience weakness, ataxia, myoclonus, migraines, nausea and vomiting and hearing loss.[241]

The variety of mitochondrial disease manifestations complicates diagnosis. Diagnostic studies may help the clinician come to a specific diagnosis. Laboratory testing of patients with mitochondrial disease may reveal elevated resting lactate and pyruvate levels with parathyroid, renal, or hepatic dysfunction. In MERRF, MELAS, and MNGIE, electrodiagnostic testing may demonstrate a myopathic or occasional neurogenic pattern.[241] Electrocardiogram may demonstrate heart block in KSS or MELAS while preexcitation is present in MELAS and MERRF.[241] Imaging of the head may show calcification and atrophy in MERRF, MELAS, and KSS.[241] Muscle histology is neither 100% sensitive or specific to diagnose all mitochondrial disorders; however, features, such as, an overabundance of mitochondria, enlarged mitochondria, inclusions within the mitochondria, abnormal histochemical or immunohistochemical stains, ragged-red fibers by Gomori trichrome stain or Southern blot genetic testing may suggest a specific mitochondrial process.[241]

Over 600 abstracts have been published regarding the treatment of mitochondrial disease. Only a limited number of these studies have been done in a randomized controlled fashion with clinically relevant primary outcomes.[239] Coenzyme Q10 (ubiquinone) has been evaluated in certain mitochondrial disorders due to the observation that patients typically have lower than normal serum levels of this substance. In 1997 the results of a randomized double-blind crossover trial study were published studying eight patients with mitochondrial disorders.[242] Patients receiving coenzyme Q10 (160 mg/day for three months) showed an increase in global MRC (medical research council) score, with a trend towards improvement in other subjective and objective measures.[239,242] An earlier double-blind crossover trial of 16 CPEO patients did not demonstrate these same benefits after nine months of 100 mg/day of coenzyme-Q10 therapy.[239,243] Still other case reports of patients with coenzyme Q10 deficiency claim benefits in strength, clinical status, fatigue, ataxia, and seizure frequency.[244] Further studies need to be completed to determine which specific mitochondrial disease coenzyme Q10 can benefit and at what dosage.

Creatine supplementation has also been utilized in mitochondrial disease. Creatine is thought to participate in the resynthesis of adenosine triphosphate, a substance that is depleted in mitochondrial disease.[245] In one randomized crossover study, seven patients with mitochondrial cytopathies were given 5g of creatine twice a day for two weeks followed by 2g two times a day for one week. There was increased handgrip strength, and isometric dorsiflexion torque while no major side effects were recorded.[246] In a conflicting report, patients with either CPEO or mitochondrial myopathy received creatine in a dosage of 20 g/day for four weeks without benefit compared to placebo, and two creatine treated patients developed muscle cramps.[239,245]

Sodium dichloroacetate is an agent that stimulates the conversion of pyruvate to acetyl-CoA and CO2 while playing a role in glucose metabolism.[247] In a double-blind, placebocontrolled, crossover trial of sodium dichloroacetate (25 mg/kg two times a day) was given to 11 mitochondrial disorder patients for one week with results showing reduced blood lactate, pyruvate and alanine levels after exercise and reductions of brain lactate/creatine ratios.[247] Unfortunately MR spectroscopy of muscle and self-assessed clinical disability scores remained unchanged in the treatment group.[247]

Other supportive treatments are often necessary in patients with mitochondrial diseases. Seizures require antiepileptic medications, while electrolyte, endocrine, and metabolic abnormalities need to be monitored and corrected. In cases of severe heart block, cardiac pacemaker placement may be life-saving.

Impairment of mitochondrial oxidative-phosphorylation pathways may elevate free radicals. Antioxidants suchas beta-carotene, vitaminC, vitamin E, alpha lipoic acid (a coenzyme naturally found in mitochondria) and CoQ10 are frequently used to decrease the formation of free radicals.[244,248] Small scale reports have claimed improved liver function, mitochondrial function, endurance, phosphocreatine recovery postexercise, and improved muscle phosphorous magnetic resonance spectroscopy (^{31}P-MRS) using antioxidant therapies.[241,244] Vitamin K1 (phylloquinone), K3 (menadione), and vitamin C have been tried based on their ability to donate electrons to cytochrome C oxidase (COX), while nicotinamide (the amide form of niacin) and riboflavin (a precursor for cofactors in complexes I and II) have been suggested as potential therapies based upon their ability to enhance electron chain function.[241,249,244] Still other agents such as idebenone (a synthetic analogue of Co-Q10, succinate (a substrate for electron transfer), triacylglycerol (a form of NADH and FADH2), thiamine (a cofactor for pyruvate dehydrogenase), and carnitine (a carrier involved in fatty acid transport) have been used in a limited fashion in patients with mitochondrial disease. Given the lack of a cure, limitations of prior research, and the difficulty extrapolating data from one mitochondrial disease to another, cocktail approaches with multiple supplements are often used in the hope of sustained benefit from severe disease.

Further studies need to be completed to validate the use of these agents in isolation and in such combinations.

Mcardle's disease (glycogen storage disease type v)

McArdle's disease is an autosomal recessive metabolic myopathy caused by a gene mutation on chromosome 11 and an absence of the glycolytic enzyme myophosphorylase.[250,251] Patients with this disease are not able to mobilize muscle glycogen stores during anaerobic metabolism and have an abnormal oxidative phosphorylation function.[250]

The clinical features of McArdle's disease often present in the second and third decades with exercise induced fatigue, weakness, myalgias relieved by rest, and occasional muscle cramps with persistent hardness of the exercised muscle.[251] Approximately one half of patients with McArdle's disease experience myoglobinuria, usually following a period of prolonged or severe exercise, with half of these patients experiencing acute renal insufficiency.[251] Some patients experience a second wind effect in which exercise may be continued after a brief rest.[251] Patients often can identify a threshold rate of exercise to permit a second wind and another rate of exertion to prevent severe muscle cramping. These patient based observations frequently serve as the basis for preventive treatment.

Diagnosis is made on clinical grounds, supported by raised plasma creatine kinase levels, and proven through the absence of muscle myophosphorylase during histochemical or biochemical evaluation.[250] Electromyography of a cramping McArdle's muscle is electrically silent due to contracture.[251] During a forearm exercise test there is a lack of a normal rise in serum lactate. This test is no longer recommended as a necessary diagnostic procedure in view of the risk of precipitating ischemic necrosis of muscle with renal failure, the lack of sensitivity and specificity in establishing the diagnosis, and the availability of molecular diagnostic testing using muscle biopsy tissue.

Until curative treatment is available, such as gene transfer of myophosphorylase, educational and supportive care are paramount in McArdle's disease. Patients can be educated about adaptive lifestyles that avoid strenuous exercise and utilize the second wind effect.

Several randomized and nonrandomized studies have attempted to evaluate glucose metabolism in patients with myophosphorylase deficiency. In 1985, a single-blind controlled trial of a female patient with McArdle's disease showed a trend towards improved grip strength after glucagon use.[250,252] Likewise, in a parallel single-blind randomize crossover study of 75g of oral sucrose versus placebo taken 30–40 minutes prior to fixed exercise, it was determined that sucrose reduced perceived exertion and maximum heart rate during exercise.[253] Glucose infusion has also been suggested to improve the second wind effect. In a study of nine patients with reduced myophosphorylase levels, patients were found to have a 20% increase in oxidative capacity when given a continuous glucose infusion during exercise.[254] None of these potential treatments have achieved sustained therapeutic results in McArdle's patients.

Treatment of patients with McArdle's disease with creatine has also occurred. A randomized double-blind placebo controlled crossover study of creatine (at 150 mg/kg/day for five days followed by 60 mg/kg/day for five weeks) led to perceived improvement of symptoms, an increased tolerance of workload, and an increased depletion of phosphocreatine during ischemic exercise.[255] In a later study, 150 mg/ kg/day of creatine compared to 60 mg/kg/day was found to not provide any additional benefit and more exercise-induced myalgia was experienced.[256] Given the results of these studies, patients with McArdle's disease often receive low-dose supplementation of creatine.

Other studies have studied the benefit of high protein diets in McArdle's disease. Unfortunately, these studies lacked the statistical power to prove or disprove benefit and have left creatine as the mainstay of treatment.[250]

Representative Diet Supplements

Coenzyme q10 (ubiquinone)

Coenzyme Q10 (CoQ10) is a lipid soluble quinine compound that shuttles electrons from complexes I and II to complex III while stabilizing the inner mitochondrial membrane oxidative-phosphorylation enzyme complex.[241,240,244] Coenzyme Q10 is produced endogenously, but can also be obtained by dietary sources found in animals.[248] In vitro, coenzyme Q10 has been shown to act as an antioxidant.[244] Its use has been proposed in many neuromuscular diseases, including numerous mitochondrial disorders, motor neuron diseases, and myopathies.

Creatine monohydrate

Creatine monohydrate is a naturally occurring substance, found in high concentration in muscle and brain. Creatine monohydrate participates in the formation of creatine phosphate, which is used for energy metabolism.[245] It can be synthesized by the liver from arginine, glycine, and methionine, or supplemented through the diet through meat products.[248] Supplementation of creatine increases intracellular phosphocreatine and anaerobic power output in healthy patients.[245,244] Elevated intracellular phosphocreatine may ultimately decrease the body's dependence on oxidative phosporylation and prevent ATP depletion.[244,248] In theory, creatine monohydrate has the ability to increase muscle force output, promote fatfree mass, enhance energy shuttling, reduce intracellular calcium accumulation, and reduce apoptosis thus providing grounds for its experimental use in mitochondrial and nonmitochondrial myopathies.[257] More research is necessary to determine the relationship between dietary intake of creatine, the associated increase in intramuscular energy stores (creatine phosphate and ATP), and side effects, such as muscle cramps. Serious side effects such renal failure and rhabdomyolysis, are rare at low dosages, but may occur in individuals taking high doses and in individuals who are dehydrated.[248]

Sodium dichloroacetate

Sodium dichloroacetate is a lactate reducing supplement that has provided benefit to patients with mitochondrial disease. Sodium dichloroacetate stimulates the activity of pyruvate dehydrogenase (PDH), which catalyzes the conversion of pyruvate to acetyl-CoA and CO_2, and promotes oxidative glucose metabolism in the mitochondria.[247] Reported side effects of sodium dichloroacetate include fatigue, shortness of breath, gastrointestinal distress and tremor.[258]

Conclusion

Pharmacological experimental therapeutics of neuromuscular disease remains an ever-expanding field shaped by thoughtful clinical trials and patient guidance. Through past research, clinicians are no longer limited to symptomatic management, but rather have a myriad of treatment options available to quell neuromuscular disease. Future studies will serve to expand scientific knowledge, identify new neuromuscular agents, and clarify existing questions regarding current neuromuscular therapies.

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Pain

Chapter: Pain
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The International Association for the Study of Pain classifies pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[1] However, the perception of pain for an individual remains very subjective and is related to nociceptive input in a very complex and poorly understood manner.[2] Nonetheless, advances in our understanding of the neuropharmacology and neurophysiology of pain and nociception have provided a more rational basis for therapy of acute and chronic pain in people.[3] This chapter will review current concepts of the mechanisms of pain and nociception and its pharmacological management.

Types of pain

Three basic types of pain in humans have been described. They often occur in combination, however, and patients may not be able to distinguish among them.

Somatic Pain

Somatic or *nociceptive* pain is a consequence of tissue injury, such as muscle, tendon, or ligament tears or strains; traumatic bone fractures; bone metastasis; or postoperative wound pain. Activation of specific sensory receptors termed *nociceptors* are responsible for this sensation.[4]Somatic pain is typically well localized and is usually familiar to the patient and easily described. It is frequently described as aching, sharp, and occasionally gnawing in quality.

Visceral Pain

This type of pain typically results from trauma, inflammation, infection, or tumor growth in thoracic or abdominal viscera. Nociceptors have been identified in visceral tissues and their activation by noxious stimuli probably accounts for the perception of visceral pain. Common examples of visceral pain include cholecystitis, pancreatitis and pancreatic carcinoma, angina pectoris, and peptic ulcer pain. Unlike somatic pain, visceral pain is usually poorly localized and often referred to cutaneous sites, which may themselves be tender, such as right shoulder pain accompanying diaphragmatic irritation in cholecystitis or the neck and left arm pain associated with myocardial ischemia. Clearly, ignorance of referral patterns for visceral pain may lead to diagnostic confusion. The neural mechanisms underlying referred pain may relate to convergence of visceral afferent input and cutaneous afferent input into common pools of somatosensory neurons in the dorsal horn of the spinal cord.[4]

Deafferentation Pain

Deafferentation pain, the third major category, is a consequence of neural injury. This type of pain is usually exceedingly unpleasant, often has a very different quality than somatic or visceral pain, and is often unfamiliar to the patient.[3,5] Typically, deafferentation (neuropathic) pain is described as squeezing or vise-like, burning, or shooting and electric-like. Typical examples include diabetic sensory neuropathies, acute zoster neuralgia and postherpetic neuralgia, plexopathies secondary to trauma or metastatic infiltration, and central, or thalamic, pain complicating stroke.

The pathophysiology of pain complicating neural injury is complex and incompletely understood. After injury to peripheral nerves, ectopic discharges have been noted at the level of peripheral nerve and within the dorsal horn and even the thalamus, which may be responsible for some components of deafferentation pain following peripheral nerve injury.[3] Evidence now suggests a role of N-methyl-D-aspartate (NMDA) receptors and nitric oxide in sensitization within the spinal cord, termed *windup*. This also is associated

with sprouting, implying anatomical changes in the dorsal horn with chronic pain. Deafferentation pain does not involve nociceptors, which may help explain its peculiar quality. Clinically, deafferentation pain is difficult to manage with conventional nonnarcotic and narcotic analgesic drugs and often is more easily treated with anticonvulsants, antidepressants, and steroids.[3] In specific cases, such as trigeminal neuralgia, anticonvulsants are clearly the agents of choice.

The sympathetic nervous system may be involved in these pain syndromes, especially deafferentation pain. Causalgia complicating peripheral nerve injury represents a distinct, sympathetically mediated pain characterized by burning, dysesthetic pain associated with dystrophic changes in the skin, subcutaneous tissues, muscles, and joints.[6] Evidence implicating the sympathetic nervous system in pain include (1) the improvement of pain and dystrophic changes with sympathetic blockade in humans or sympatholytic drugs, (2) the worsening of pain with sympathetic stimulation in patients with causalgia, (3) the appearance of new alpha-adrenergic receptors on regenerating nerve sprouts following injury in animal studies, (4) the demonstration of interactions between sympathetic efferent fibers and nonnociceptive afferent fibers and wide-dynamic range neurons in the dorsal horn following trauma, and (5) microneurographic studies in humans that correlate the sensation of hyperpathia with the local application of norepinephrine and increased activity in C-fiber nociceptive units.

Acute versus chronic pain

Clinically, it is important to distinguish acute from chronic pain. Acute pain usually has a well-defined onset and is often associated with a readily definable cause. Objective physical signs of autonomic nervous system (ANS) activity, such as tachycardia, pupillary dilation, diaphoresis, and hypertension often occur concurrently. These signs serve to substantiate the patient's subjective report of pain. Acute pain is best managed by treating the underlying cause, thereby allowing the tissue to heal. Temporary relief may be obtained by administering analgesic drugs, both opiate and nonnarcotic.

The point at which acute pain becomes chronic is arbitrary, but is generally considered to be six months. Unlike the acute variety, chronic pain is often unassociated with autonomic nervous system activity, and the temporal onset and etiology are often obscure. Chronic pain may be associated with symptoms and signs that mimic depression and is often complicated by environmental and emotional factors that prolong pain in the absence of tissue damage. One cannot assume that the complaint of pain is due to depression, however. With few objective signs substantiating the report of chronic pain, the patient may not look as if he or she is experiencing any discomfort, leading the inexperienced physician to assume mistakenly that the patient is malingering. The treatment of chronic pain is based on identifying any potential causes of ongoing tissue damage, recognizing the significant affective and environmental factors that may contribute to the patient's pain experience, and then using psychological, behavioral, and pharmacological therapies to help the patient to maintain personally meaningful activities without risking further harm. Chronic cancer pain, unlike chronic pain of nonmalignant origin, often has a definable cause of ongoing tissue injury and is best treated like acute pain. For these reasons, it is best considered as persistent acute pain.

Anatomy and physiology of central nociceptive systems

Nociceptors

Sensory receptors that respond to noxious or tissue-damaging stimuli can be found in skin and subcutaneous tissues, muscles, joints, and abdominal and thoracic viscera.[7] These nociceptors are defined by their morphologic characteristics and physiologic responses to noxious chemical, mechanical, or thermal stimuli. Myelinated nociceptors respond almost exclusively to mechanical stimuli while somatovisceral nociceptors are free, unencapsulated nerve endings of Aδ and C-fibers. Although cutaneous nociceptors are not spontaneously active, they may sensitize within minutes after injury.[8] Sympathetic activity also may sensitize nociceptors,[9] an interesting observation in view of the relationship between the sympathetic system and causalgia.

Light myelinated Aδ or unmyelinated C-fibers conduct nociceptive afferent impulses. Microneurography studies reveal that activation of a single myelinated nociceptor is sufficient to cause pain, often described as sharp and stinging in quality. Stimulation of unmyelinated nociceptor afferents at frequencies greater than 1.5 per second is associated with dull, burning, or aching pain.

Dorsal Horn and Spinothalamic Tracts

Nociceptive afferent fibers have their cell bodies in the dorsal root ganglia, with both peripheral and central projections. These fibers terminate in the dorsal horn of the spinal cord with as many as 25% to 30% of unmyelinated ventral root fibers carrying nociceptive information in humans. The dorsal horn consists of six lamina, with lamina I, the marginal zone, being most dorsal (Figure **11–1**).[10] Nociceptive fibers, including those in the ventral root, synapse principally in laminae I, II, and V.[7] Aδ afferents synapse predominately in laminae I and V, while C-fiber afferents synapse directly in laminae II (the substantia gelatinosa) with polysynaptic relays into lamina V as well.[7] The substantia gelatinosa can be subdivided into outer (IIL) and inner (II) laminae, with lamina IIo receiving some Aδ nociceptive input as well as nociceptive C-fiber input; lamina II, receives no Aδ input and is innervated by predominately non-noxious C-fiber (mechanical and thermal) fibers. Laminae III and IV receive largely nonnociceptive, large-fiber mechanoreceptor Aβ fibers, and lamina VI receives no important nociceptive projections.[11] Neurons in laminae I and II are predominately nociceptive-specific, and respond to a narrow range of noxious thermal, mechanical, or chemical stimuli, whereas neurons in lamina V, which receive major inputs from non-noxious and noxious afferents, may respond to diverse sensory input and are termed *wide dynamic range* cells. Both types of neurons are important in encoding for pain. The substantia gelatinosa cells exert minor excitatory and major inhibitory effects at the local segmental level.

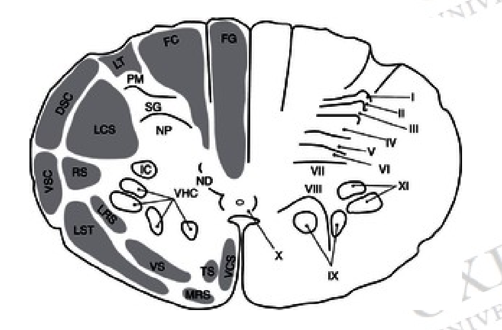


Figure 11–1.
Cross section of the spinal cord at approximately the C-8/T-1 segmental level. Tracts and nuclei of the cord are illustrated on the left; Rexed's laminar organization of the gray matter is illustrated on the right. Abbreviations: DSC = dorsal spinocerebellar tract; FC = fasciculus cuneatus; FG = fasciculus gracilis; IC = intermediotolateral cell column; LCS = lateral corticospinal tract; LT = Lissauer's tract; MS = medial reticulospinal tract; ND = nucleus dorsalis; NP = nucleus propius; PM = posteromarginal nucleus; RS = rubrospinal tract; SG = substania gelatinosa; TS = trectospinal tract; VCS = ventral corticospinal tract; VHC = ventral horn cell columns; VS = vestibulospinal tract; VSC = ventral spinocerebellar tract. (From Gilman, S, Newman, SW. Manter and Gatz's essentials of clinical neuroanatomy and neurophysiology. 7th ed. Philadelphia: FA Davis; 1987, 16, with permission).

A small fraction of substantia gelatinosa cells contribute axons to the ascending spinothalamic tract. Although axons from most cells in the dorsal horn contribute fibers to the ascending spinothalamic tracts, the predominant projections arise from cells in laminae I and V (Figure **11–2**). The spinothalamic tract may be divided into two distinct

physiological systems that may be responsible for the phenonmenon of first and second pain. The neospinothalamic tracts receive principally Aδ and C-fiber input respectively, a subdivision thought to be responsible for the phenomenon of first and second pain.[2,12] For example, after cutaneous noxious stimulation by a pin, a well-localized prickling sensation is conveyed by Aδ neospinothalamic activity, followed by a less well-localized, more unpleasant second pain sensation thought to be conveyed by C-fiber paleospinothalamic afferent activity. Interestingly, it is this second pain component that is sensitive to opioids.

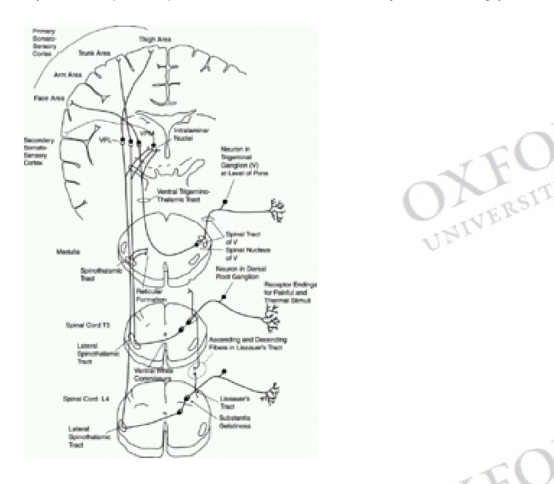


Figure 11–2.
The central nervous system pathways that mediate the sensations of pain and temperature. (From Gilman, S, Newman, SW. Manter and Gatz's essentials of clinical neuroanatomy and neurophysiology. 7th ed. Philadelphia: FA Davis; 1987, 16, with permission.)

The neospinothalamic tract is a monosynaptic tract that projects to the ventroposterolateral nucleus of the thalamus and from there to the somatosensory cortex (Figure **11–2**). It is topographically organized, overlaps with fibers conveying light touch sensation, and provides information concerning the quality, intensity, and location of noxious stimuli. In contrast, the paleospinothalamic tract, which is not topographically organized, is polysynaptic, with many projections into the brain-stem reticular formation. It terminates in the medial and posterior thalamic nuclei. Medial and intralaminar thalamic nuclei also receive efferents from the striatum, and it is speculated that this area of the thalamus may be involved in the reflex motor responses that often accompany painful stimulation.[2] Many of these thalamic cells receive convergent input from the skin, muscles, and viscera, perhaps explaining in part the phenomenon of referred pain. After terminating in the thalamus, paleospinothalamic fibers project to diffuse limbic cortical and subcortical areas. This tract subserves the affective-motivational and suffering aspects of pain perception.

Mechanisms of Facial Sensation

The spinal trigeminal nucleus and adjacent reticular formation are directly continuous with the dorsal horn of the cervical spinal cord, and serve as the anatomic and physiologic equivalent of the dorsal horn.[13] Descending fibers in the spinal trigeminal tract convey nociceptive and nonnociceptive information for the ipsilateral face; forehead; and mucous membranes of the nose, mouth, and oral cavity. A subdivision of the spinal trigeminal nuclear complex, the subnucleus caudalis, is uniquely concerned with pain and thermal sensation and has a laminated structure analogous to the dorsal horn. Laminae I and V of this nucleus encode nociceptive information in a manner similar to the spinal dorsal horn. Second-order neurons ascend to the contralateral ventroposteromedial thalamic nucleus as part of the medial lemniscus. Thus, the neural processing of facial and cranial nociceptive stimuli is entirely analogous to spinal mechanisms.

The Cortex and Pain

The role of the cerebral cortex in pain remains controversial. Although one can identify nociceptive-specific neurons in the primate cortex, clinical effects of cortical lesions on pain perception remain enigmatic. Imaging studies have suggested a role fo the cingulated cortex in pain perception.[14–18]

Antinociceptive systems in the cns

The perception of nociceptive input in humans is highly dependent on the situation in which it occurs. Although the brain is continually bombarded with a variety of sensory stimuli, it retains the ability to focus on specific inputs without attending to others. Evidence from a variety of sources indicates that the central nervous system (CNS) has the ability to filter nociceptive input. When Beecher[19] compared the analgesic requirements of soldiers wounded during World War II to civilians undergoing surgery in the United States, he found that the soldiers required less medication despite their more extensive injuries. Endogenous pain-modulating systems capable of alleviating the perception of nociceptive input have been identified and extensively studied both physiologically and pharmacologically.[20–27]

Electrical stimulation of the periaqueductal gray (PAG), a region subsequently found to contain high levels of opioid peptides and receptors[22] elicits a strong analgesia both in animals and in humans.[28–31] These actions are due, at least in part, to activation of descending systems of the nucleus raphe magnus.[32] The microinjection of morphine into the PAG also produces analgesia,[22] whereas naloxone antagonizes both stimulation-produced analgesia and morphine analgesia from this region, implying that stimulation-produced analgesia results from the release of opioid peptides.

At the level of the spinal cord, both descending systems from the brainstem and local systems within the cord greatly influence nociceptive modulation. In the dorsal horn, small-diameter, primary afferent fibers terminating in lamina I and the outer substantia gelatinosa contain significant levels of substance P, a peptide thought to be important in pain transmission.[33,34] The complexity of spinal cord systems is illustrated by the large number of transmitters within the substantia gelatinosa, including enkephalins, bombesin, cholecystokinin, vasoactive intestinal polypeptide, neurotensin, and somatostatin; virtually all are able to modulate pain perception. Additional transmitters involved with pain modulation within the CNS include acetylcholine, norepinephrine, dopamine, serotonin, γ-aminobutyric acid (GABA), substance P, and adrenocorticotropic hormones. Although many of these drugs can influence pain perception, their actions are often limited and can-not compare to the potency of the opioid systems.

Endogenous Opioid Systems

The CNS contains complex opioid systems important in a wide spectrum of nervous system actions, of which pain perception is only one. In general, the localization of these peptides and their receptors correlates extremely well with those areas of the CNS described previously that have been implicated in pain perception. However, their presence in other brain regions emphasizes their wider importance in CNS function. Thus, the complexity of the endogenous opioid systems equals, or even exceeds, that of other classes of transmitters.

Endogenous opioids

The enkephalins are pentapeptides that share their first four amino acids and have either methionine or leucine as the fifth (Table 11–1). The additional opioid peptides, including the dynorphins and ß-endorphin, incorporate the sequence of either [Leu5]enkephalin or [Met5]enkephalin at their N-terminus. Despite the similarity in amino acid sequence, the precursors of the enkephalins and the other endogenous opioid peptides are discrete gene products with distinct regional distributions and pharmacologies.[35]

Table 11–1 Endogenous Opioids

Natural opioid peptides	
[Leu5]enkephalin	**Tyr-Gly-Gly-Phe-Leu**
[Met5]enkephalin	**Tyr-Gly-Gly-Phe-Met**
Dynorphin A	**Tyr-Gly-Gly-Phe-Leu**-Arg-Arg-Ile-Arg--Pro-Lys--Leu-Lys-Trp-Asp-Asn-Gln
Dynorphin B	**Tyr-Gly-Gly-Phe-Leu**-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr
α-Neoendorphin	**Tyr-Gly-Gly-Phe-Leu**-Arg-Lys-Tyr-Pro-Lys
ϟ-Neoendorphin	**Tyr-Gly-Gly-Phe-Leu**-Arg-Lys-Tyr-Pro
$ϟ_h$-Endorphin	**Tyr-Gly-Gly-Phe-Met**-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu
Endomorphin-1	Tyr-Pro-Trp-Phe-NH_2
Endomorphin-2	Tyr-Pro-Phe-Phe-NH_2
Orphanin FQ/Nociceptin	**Phe-Gly-Gly-Phe**-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asp-Glu
Synthetic Opioid Peptides	
DPDPE	[D-Pen2, D-Pen5]enkephalin
DADLE	[D-Ala2, D-Leu5]enkephalin
DALDA	Tyr-D-Arg-Phe-LysNH_2
DAMGO	[D-Ala2,MePhe4,Gly(ol)5]enkephalin
DSLET	[D-Ser2,Leu5]enkephalin-Thr_6
Deltorphin II	Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH2
CTOP	D-Phe-c[Cys-Tyr-D-Trp-Orn-Thr-Pen]-Thr-NH_2

The common enkephalin sequence in the natural peptides is bolded.

Neurotransmitters are inactivated within the brain either by reuptake and/or through enzymatic degradation (see Chapter 1). There is no convincing evidence for up-take of opioid peptides and inactivation is rapidly achieved by a series of peptidases. Substitution of the second amino acid, glycine, with D-amino acids, such as D-alanine, greatly stabilizes the peptides to proteolytic cleavage. The endogenous opoioid peptides are potent analgesics, although their study initially was difficult due to their rapid degradation. Over the years, many synthetic peptides highly selective for mu and delta receptors have been synthesized. An alternative approach in analgesic development has been the development of inhibitors of these enkephalinases.[36,37] However, the activity of these agents is dependent upon the underlying toniclevel of enkephalin release and they have had only modest activity. The opioid peptides and their receptors are often present in neurons containing substance P and CCK. This colocalization is interesting in view of the influence many neurotransmitter systems have on opioid analgesia.

Opioid Receptors

Early binding studies quickly established an excellent correlation between the affinity of opiates in binding assays and their pharmacologic potency in vivo.[38,39] Compounds with little analgesic activity had poor affinities at the receptor, including inactive opiate stereo-isomers. Binding sites were associated with nervous tissue and within the brain and spinal cord showed a regional distribution closely associated with areas known to be important in opiate analgesia, such as the periaqueductal gray (PAG) and medial thalamus within the brain and the substantia gelatinosa at the spinal cord level. Localization of these sites to additional regions, such as the striatum, suggest a more general role for these receptors beyond simply pain modulation.[20]

Detailed pharmacological studies suggested three major families of opioid receptors: mu, delta and kappa. Each had its set of selective ligands and unique binding profiles and pharmacology (Table 11–2).

Table 11–2 Tentative Classification of Opioid Receptors

Family	Gene	Drugs
Mu	MOR-1	Morphine, endomorphin 1 and 2 ß-Endorphin
Delta	DOR-1	Enkephalin ß-Endorpin
$Kappa_1$	KOR-1	Dynorphin A, U50488H, U69,593
$Kappa_2$	KOR-1/DOR-1 dimer	No selective agent
$Kappa_3$	Not known	Naloxone benzoylhydrazone, Levorphanol

All the receptors listed here can elicit analgesia. Other side effects can vary.

Mu receptors

Morphine (Figure **11–3**) produces is actions, including analgesia, constipation, and respiratory depression, through mu receptors, which initially were defined by their binding selectivity. Pharmacological studies using antagonists implied the existence of multiple classes of mu receptors.[40,41] The mu receptor MOR-1 was cloned in the early 1990s[42–45] and is a member of the G-protein coupled receptor family. It is comprised of four exons, with the fourth responsible for only the last 12 amino acids at the C-terminus (Figure **11–4**). With only a single gene, it was initially difficult to understand the pharmacological studies implying multiple mu opioid receptors. However, in recent years, a host of full length, functional splice variants of MOR-1 have been isolated from mouse, rat and humans in which exon 4 in MOR-1 is replaced by a collection of alternative exons (Figure **11–4**).[46–53] It is interesting that the amino acid sequence defining the binding pocket of all the human variants, which are encoded by exons 1–3, are identical The only differences are at the tip of the intracellular C-terminus, a region important in coupling to transduction system (Figure **11–4**).[46–53] Thus, it was not surprising that all the human variants showed similar affinities for opioids and high mu selectivity.

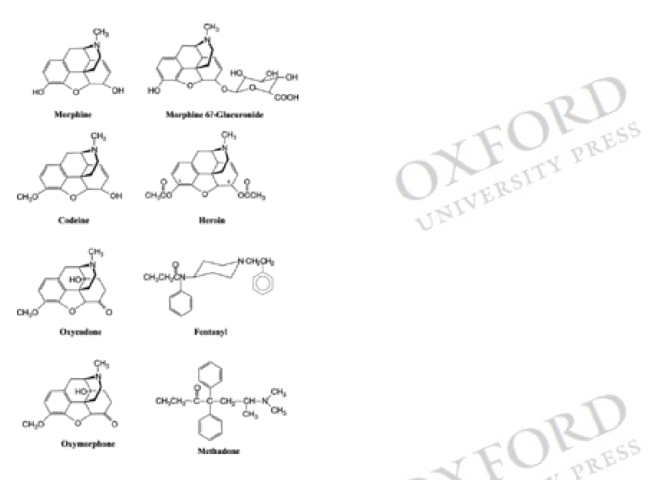


Figure 11–3.
Structures of commonly used opioids.

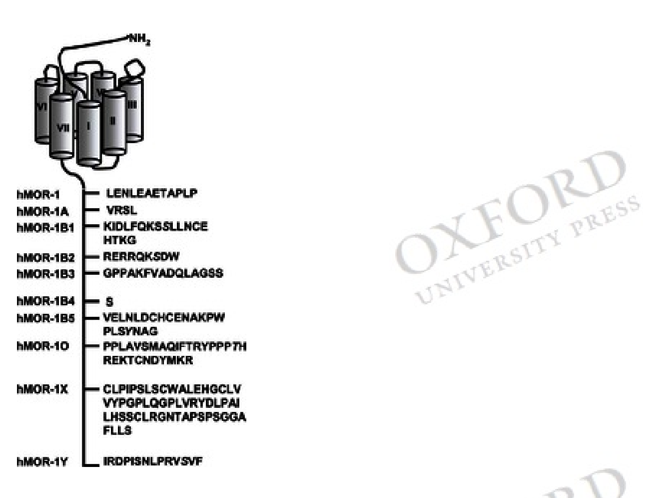


Figure 11–4.
Diagram of the structure of the human mu opoid MOR-1 receptor with functional splice variants in which exon 4 is replaced by a collection of alternative exons

The presence of multiple mu opioid receptors may also help explain a number of clinical observations. For example, patients often show incomplete cross tolerance to mu

opioids,[54] an observation that has been replicated in animal models.[55] It also may help explain the wide range of sensitivity of patients to various mu opioids. This is well illustrated by studies with the CXBK mouse.[56–59] This mouse is insensitive to morphine, requiring doses 5–10-fold higher than those in standard strains to produce analgesia. Yet, the CXBK mouse retains full analgesic sensitivity to a wide range of other mu opioids, including fentanyl, methadone and even heroin. Knockout studies also illustrate the differences between the different mu opioids. In a knockout mouse with disruption of exon 1, morphine is inactive at doses up to 20-fold higher than those active in wildtype controls.[60] Yet, these knockout animals still respond to heroin and several other mu opioids, including morphine-6ß-glucuronide. Thus, the existence of multiple mu opioid receptors may help explain the wide variability of patient responses among the different mu opioids and the need to individualize therapy.

Delta receptors

The discovery of the enkephalins soon led to the identification of the delta receptor.[61–63] These receptors are highly selective for enkephalins, displaying poor affinity for mu ligands. The delta receptor DOR-1 was the first opioid receptor to be cloned.[64,65] Like the mu receptor, DOR-1 encodes a traditional G-protein coupled receptor. Although pharmacological studies had suggested subtypes of delta receptors, these have not been identified at the molecular level. Delta receptors have a unique regional distribution[24,66] and pharmacology, but still can elicit analgesia. However, there are no clinically available delta drugs as yet.

Kappa receptors

Kappa receptors were initially proposed from in vivo studies based on a number of benzomorphan derivatives;[67] binding and pharmacologic evidence now has uncovered several kappa receptor subtypes.[68] $Kappa_1$ receptors are best defined by their selectivity for the agonist U50,488H and the antagonist nor-binaltorphimine. Both $kappa_2$ and $kappa^3$ receptors are U50,488H-insensitive, but differ significantly from each other in their overall binding profile. Dynorphin A is traditionally considered to be the endogenous ligand for $kappa^1$ receptors.

$Kappa_2$ receptors also were initially proposed from in vivo studies. However, recent work now suggests that the $kappa_2$ receptor actually corresponds to a dimer between the delta receptor DOR-1 and the $kappa^1$ receptor KOR-1.[69] However, the pharmacology of this site remains unclear since there are no selective drugs to use in vivo.

$Kappa_3$ receptors were defined pharmacologically and through receptor binding assays well before the traditional opioid receptors were cloned.[70–72] Naloxone benzoylhydrazone has been successfully used to define the site and its pharmacology. Several clinically important drugs, such as levorphanol, have activity at this site, as well as at mu sites. Although there is evidence that the receptor is closely related to the orphanin FQ receptor ORL1 receptor,[73] the full length $kappa^3$ receptor has not yet been cloned.

Other classes of opioid receptors

A large number of opioid peptides have been identified and it is reasonable to anticipate that many will have their own selective receptors. The first example arose several years ago, the sensory neuron specific receptor, which is selective for bovine adrenal medulla 22 (BAM22).[74–76] It will be interesting to see how many additional receptors are uncovered in the future.

Opiate Actions

Understanding the pharmacologic actions of an opiate is dependent on knowing its receptor profile. Few drugs interact with a single receptor. Thus, the pharmacology of a drug is actually the summation of its interactions with all the receptors to which it binds. In addition, as the dose of drug is increased, it will interact with an increasing number of receptors as it labels sites for which it has lower affinity.

Opiate analgesia

Opiates elicit analgesia at several sites within the neuraxis. Opioid receptors have been demonstrated on peripheral nerves, as well as regions known to be important in pain processing, such as the dorsal horn of the spinal cord, a number of brainstem nuclei such as the periaqueductal gray, nucleus raphe magnus and locus ceruleous. Administration of morphine or other mu opioids to any of these regions can elicit a profound analgesia. However, this effect can be markedly potentiated if several sites are activated at once.[77–79] Obviously, drugs given systemically will have access to all the sites. However, increasing the dose of a drug at a specific site may enhance this potentiation. An excellent example is the use of epidural opioids, which are commonly used in a wide range of clinical situations. Epidural administration leads to high levels of drug within the CSF surrounding the spinal cord. In addition, there is significant systemic absorption as well. In a mouse model, administration of morphine intrathecally at doses that elicit little analgesic activity can shift the systemic dose-response curve markedly to the left (Table 11–3).[79] Indeed, administering an intrathecal dose of morphine only 15% of its intrathecal ED50 lowered the required systemic dose to provide analgesia by 10-fold. Interestingly, these interactions are limited to analgesia, leading to an increased therapeutic index with regards to many side-effects.

Table 11–3 Synergy Between Spinal and Systemic Morphine in an Animal Model

Treatment	ED_{50} value	ED_{50} shift
Systemic morphine alone	3.1 mg/kg	
Spinal morphine alone	305 ng	
Systemic morphine ED_{50}		
+25 ng morphine i.t.	0.5 mg/kg	6
+50 ng morphine i.t.	0.3 mg/kg	10
+100 ng morphine i.t.	0.2 mg/kg	15
+200 ng morphine i.t.	0.04 mg/kg	78

Note: The ED50 for morphine was determined following either systemic administration (s.c.) or intrathecal (i.t.) administration. Then, the ED_{50} value for systemic morphine was determined following the addition of the indicated dose of intrathecal morphine. Results adapted from Kolesnikov and colleagues.[79]

All three classes of opioids can elicit analgesia, both peripherally and centrally. However, the mu system has been most extensively studied and is the most robust. Most clinically used opioids act through mu systems. However, not all patients respond equally well to all mu opioids. While one patient may respond better to one drug, other patients may do better with a different one. The mechanisms involved remain unclear, but likely reflect pharmacogenetic differences among patients. Some of these involve metabolism, both enhancing and diminishing activity. For example, morphine is converted to morphine-6ß-glucuronide, a metabolite far more potent than morphine, while

codeine needs to be demethylated to morphine for activity. Alternatively, metabolism may inactivate the agent.

A second component of the pharmacogenetics of these agents involves the splice variants. There are currently at least eleven full length splice variants of the mu opioid receptor MOR-1 in humans. As noted earlier, they all contain the same binding pocket, explaining their similar affinities for mu opioids and their selectivities. However, efficacies for mu drugs vary from one variant to another. Indeed, the rank order of both potency and efficacy of various mu drugs differs when comparing one MOR-1 splice variant to another. This may help explain some of variable responses among the drugs. Although the mu drugs will label all the variants with similar high affinities, their relative ability to activate the receptors will vary. Since the effects of a drug is the summation of its activation of all these variants and since each drug varies in its relative potency/efficacy for the different variants, the overall profile of each drug may display subtle differences from each other. In addition, there is always the possibility of mutations that selectively alter the

There are several $kappa_1$ drugs, such as pentazocine. However, most of these agents are also partial agonists at mu receptors, markedly limiting their utility in patients previously on mu opioids where they may precipitate withdrawal. Several highly selective $kappa_1$ drugs have been developed and looked at clinically, but not developed due to side-effects such as their propensity to induce psychomimetic effects and their profound diuresis. $Kappa_3$ drugs differ from the others. The most widely used $kappa_3$ agent levorphanol. Like many drugs within the kappa category, levorphanol is a mixed agent that also acts at mu receptors as an agonist.[80,81] There are no approved drugs that act through delta receptors, although preclinical evidence suggests that delta agents have analgesic activity,

Opiate tolerance

With continuous use, opiates lose their effectiveness, a process termed *tolerance*. Alternatively, it has been described as the need to escalate the dose of drug to maintain an effect. It is a physiological response and is seen in all patients. It is most prominent early in the course of therapy and may not be noticed as doses are titrated to obtain pain control. Interestingly, tolerance appears be able to reach an equilibrium state in which patients can be maintained on fixed doses of drug for prolonged periods of time without further escalation, although these doses are typically higher than those used in naïve patients. The mechanisms responsible for tolerance are complex, ranging from molecular modification of the receptor itself to compensatory pathways within the nervous system. In animal models, tolerance can be attenuated by blockade of NMDA receptors or neuronal nitric oxide synthase.[82] Even delta opioid systems appear important since morphine tolerance is lost in mice lacking a delta receptor due to a disruption of the DOR-1 gene (i.e., knockout) or lacking enkephalin due to the elimination of its gene.[83] Tolerance develops to all opioid actions, although not at the same rate or to the same degree. Many clinicians believe that tolerance to the gastrointestinal effects typically develop more slowly and to a less extent than to analgesia, narrowing the therapeutic index.

Cross tolerance among the opioids occurs, but it is not always complete. This is readily demonstrated clinically. Switching highly tolerant patients from one opioid analgesic to another often restores effectiveness of the second drug at doses far below those anticipated based upon the relative potencies of the drugs in naïve patients. In other words, the relative potencies of opioids in tolerant patients differ from their relative potencies in naïve patients. Indeed, when switching a tolerant patient from one drug to another, it is common practice to lower the calculated equivalent dose by 50% or more and then slowly titrate upwards. Similar findings have been confirmed in animal studies.

Incomplete cross tolerance is easily understood when moving from a mu opioid to a mixed mu/kappa opioid, like levorphanol.[81] Whereas morphine interacts relatively selectively with mu receptors, levorphanol acts through a combination of mu and kappa receptors. Animals tolerant to morphine showed little cross-tolerance toward levorphanol, since the morphine-treated animals were tolerant only at mu receptors, leaving the sensitivity of the $kappa_3$ receptors intact. Animals tolerant to levorphanol, on the other hand, demonstrated cross-tolerance to morphine, since the chronic levorphanol treatment produced tolerance to both mu and $kappa_3$ receptors.

Incomplete cross tolerance also exists among mu opioids. Initially, these observations were hard to understand since the drugs were assumed to act through a single receptor. However, incomplete cross tolerance was clearly observed clinically and in animal models. Indeed, clinicians utilize incomplete cross tolerance in Opioid Rotation, where patients are moved from one opioid to another when tolerance leads to side-effects that preclude further escalation of drug.[54] Recent work on the molecular biology of the mu receptor may now help explain these clinical observations. Early work from binding studies and pharmacological studies utilizing selective antagonists led the suggestion of multiple mu opioid receptors over 25 years ago.[84] Now, a number of splice variants of the mu opioid receptor MOR-1 have been isolated and characterized. Although they all derive from a single gene, there are at least 11 MOR-1 variants in humans, with even more in mice and rats.

Respiratory depression and other opiate actions

Opioids produce a variety of actions other than analgesia, most of which are not desired in the treatment of pain. The most problematic include respiratory depression, the inhibition of gastrointestinal transit that is manifested as constipation and sedation.

Respiratory depression is the most worrisome to the clinician, even though it rarely presents a problem in the outpatient setting in the absence of significant underlying pulmonary disease. Patients are more concerned by the constipation and sedation associated with these drugs, particularly since tolerance often develops more slowly than to analgesia. There is hope that agents working through delta receptors may have a different side-effect profile, but these drugs are not available. All the mu drugs induce the same constellation of side-effects. Constipation can be treated with laxatives and sedation with stimulants. However, several new agents may soon be available to help with peripherally mediated side-effects. Alvimopan and N-methylnaltrexone are peripherally selective opioid antagonists. Alvimopan is given orally while methylnaltrexone can be give parenterally. Both agents appear to help with the inhibition of gastrointestinal transit seen with opioid use. However, the selectivity of both agents is due to their limited access to central sites of action and not to a selective receptor-specific selectivity.

There may be alternative approaches towards the management of mu opioid side-effects. Early studies with the highly selective mu antagonists naloxonazine and naloxazone revealed the selective blockade of analgesia without an appreciable effect on respiratory depression or the inhibition of gastrointestinal transit.[85–88] These actions correlated with the ability of the drugs to selectively block a unique site in traditional receptor binding assays. Indeed, these observations were the foundation for the first suggestion of multiple mu opioid receptors.[84] In this hypothesis, mu sites were divided into naloxonazine-sensitive (mu_1) and naloxonazine-insensitive (mu_2) actions. The ability to selectively target specific subtypes of receptors has led to many advances in drug development. Thus, the separation of morphine analgesia from respiratory depression, inhibition of gastrointestinal transit and even many aspects of physical dependence opens the possibility of selective analgesics lacking these actions. The cloning of the various MOR-1 variants illustrates a complexity that far exceeds that initially envisioned with the first proposal of multiple mu opioid receptors. It now will be very interesting to see how these pharmacologically-defined actions will correspond to the cloned receptors.

Physical dependence and addiction

One of the major concerns regarding the prolonged use of opiates is the production of physical dependence and addiction. These are not the same and it is important to distinguish between them. Physical dependence is seen in all patients and is a physiological response to exposure to opioids. Discontinuing the opioid abruptly or challenging with an antagonist such as naloxone precipitates a well-described constellation of signs and symptoms collectively termed *opiate withdrawal*. These include anxiety, nervousness, irritability, chills alternating with hot flashes, salivation, lacrimation, rhinor-rhea, diaphoresis, piloerection, nausea, vomiting, abdominal cramps, insomnia, and, rarely, multifocal myoclonus. The abstinence syndrome can be avoided by slowly lowering the dose by 50% every several days until low doses are reached, after which the medication can be discontinued. Occasional patients require a slower decrease. In animal models even more rapid declines can be used without precipitating withdrawal. However, it is usually recommended that a slower taper be used clinically. Should symptoms occur, they can be relieved with small increases of drug. The syndrome associated with dependence and withdrawal is seen with mu agents and may differ with selective kappa and delta drugs if they become clinically available.

Addiction is very different from dependence. Whereas all patients will be dependent with chronic opioid use, very few will become addicted.[89] Addiction involves a pattern of compulsive drug use characterized by a continued craving for the drug and the need to use an opioid for effects other than pain relief. The addict exhibits drug-seeking behavior, leading to overwhelming involvement with the use and procurement of the drug. Although most patients with psychologic dependence are also physically dependent, the reverse is uncommon when using opioids for management of pain. However, physicians using these agents must always maintain a close relationship with their patients

and look for possible evidence of opioid misuse.[90] Although the inappropriate use of these drugs remain a concern, few patients being treated for medical purposes progress to addiction and this fear should not interfere with the appropriate use of analgesics.

Pharmacologic management of pain

Pain is a symptom. The most effective management of pain involves treating its underlying cause. However, inadequate pain control may preclude optimal diagnostic testing, thereby delaying the diagnosis and treatment of the disorder. Further, acute pain may complicate medical or surgical treatments. Although a variety of nonpharmacologic approaches are available, drug therapy remains the mainstay of treatment of acute pain and chronic cancer-related pain. Drug therapy of pain has improved, but is often limited by misconceptions and ignorance concerning the basic and clinical pharmacology of analgesic drugs, particularly opioids.

Analgesic drugs can be divided into three major classes for the purposes of this overview: (1) the nonsteroidal anti-inflammatory drugs (NSAIDs), which act through the inhibition of cyclooxygenase both peripherally and centrally; (2) opioids that act through their receptors described earlier; and (3) adjuvant analgesics, which can be effective in certain pain states or in conjunction with other analgesic classes. The choice of the specific drug approach is based on an assessment ofthe pain syndrome, the severity of the pain, and an understanding of the clinical pharmacology of specific analgesics.

Clinical Use of NSAIDs

The NSAIDs are useful as general purpose analgesics in mild-to-moderate pain, particularly with tissue inflammation.[91] Unfortunately, the analgesic ceiling effect of this class of agent can limit their utility in severe pain. Most of the available agents are nonselective, blocking both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2), explaining their antipyretic, antiplatelet, and anti-inflammatory effects. A number ofCOX-2 selective drugs have been developed that have greatly diminished GI toxicity, but there is evidence implicating their long-term use with cardiovascular issues. Indeed, there is now evidence suggesting that even some of the nonselective NSAIDs may have cardiovascular risk. Indeed, many of the COX-2-selective blockers have now been removed from the market. At present, celecoxib is the only COX-2 inhibitor available, limiting the use of this class of agent in patients particularly sensitive to their gastrointestinal side-effects or who are on anticoagulants.

Initially thought to act through peripheral mechanisms, reports have now suggested a central component of their activity as well. Specific NSAIDs differ in their pharmacokinetics and duration of analgesia.[91] Ibuprofen and fenoprofen have short half-lives similar in duration as aspirin, whreas diflunisal and naproxen have longer longer durations of action and can be administered twice a day. Prolongation of the bleeding time may occur due to inhibition of platelet cyclo-oxygenase and reduced formation of thromboxane A_2. Gastric irritation also occurs commonly with this class of drugs. Anecdotally, clinicians have observed that the analgesic activity of these agents may vary among patients, with some drugs working better in some while a different drug is superior in others. Thus, the choice of agent is empiric. Choices are often made based upon the efficacy of the drug in an individual patient and the side-effect profile of the drug in the patient.

Acetaminophen is also grouped in this class. It is roughly equipotent to aspirin in its analgesic and antipyretic potency, but has no anti-inflammatory or antiplatelet effects. Although acetaminophen lacks many of the gastrointestinal and antiplatelet activities, very high doses of acet aminophen greater than 4 g/day have been associated with hepatotoxicity and higher doses can be fatal. Choline magnesium trisalicylate (Trilisate) is also an effective analgesic that lacks antiplatelet effects and has fewer gastrointestinal side effects than aspirin.

Nonsteroidal anti-inflammatory analgesics, particularly indomethacin, may have a unique role in the managing bone pain secondary to tumor metastasis.[92] With the exception of acetaminophen and perhaps choline magnesium trisalicylate, however, the use of NSAIDs in oncology is limited by their effects on platelet function, which may increase the risk of bleeding problems in patients with thrombocytopenia and coagulation defects.

Clinical Use of Opioid Analgesics

Opioid analgesics are indicated to manage moderate to severe pain. They are widely used for acute pain syndromes and for cancer pain, although their utility in nonmalignant chronic pain is increasing. Unfortunately, misconceptions by both patients and caregivers regarding tolerance, physical dependence, and psychologic dependence (addiction) have limited their use. When used properly, however, opioids can be very effective in the vast majority of patients.

The potential misuse of licit opioids raises concerns throughout all levels of health-care professionals and has been a major issue politically. In most populations of patients, inappropriate opioid use does not interfere with the use in pain management.[89] However, as the use of opioids has extended to include a wide range of chronic pain syndromes, there is evidence that misuse is more common,[93] although this can be minimized by maintaining a close relationship with the patient and taking care to identify potential indications of misuse.[90]

Any patient chronically taking opiates will develop both tolerance and physical dependence. The degree of both is related to both the dose and duration of treatment, with tolerance often beginning soon after initiating therapy. Although tolerance occurs in association with physical dependence, neither implies psychologic dependence, or addiction. Both tolerance and physical dependence are normal physiologic responses that should not interfere in the use of opioids.

The first sign of tolerance is a decrease in the duration of effective analgesia, but increasing analgesic requirements in cancer patients should always raise the possibility of disease progression. Once tolerance develops, switching patients to an alternative opiate may restore analgesic sensitivity due to incomplete cross-tolerance among the opioids, including the mu-selective drugs. The equianalgesic tables used clinically were determined in naïve subjects. As patients become tolerant to one drug, however, they may retain a greater level of sensitivity toward the second due to incomplete cross-tolerance. This results in different equianalgesic ratios for the opioids in tolerant and naive patients. Thus, when switching a tolerant patient from one opioid to another, most clinicians will calculate the corresponding dose using the naïve equianalgesic ratios and decrease the calculated dose by 25%–50%.

General guidelines in the use of opioid analgesics

A number ofgeneral issues should be considered when administering opiates in the management of severe pain (Table 11–4). Pain is a subjective sensation that can only be assessed by asking the patient. While the presence of many of the autonomic signs seen in acute pain can be helpful, their absence, particularly in chronic pain patients, does not indicate the absence of pain. The autonomic signs attenuate over time despite the presence of severe pain. Furthermore, the sensitivity of patients to analgesics can vary widely. Similar observations have been made in preclinical studies, where the sensitivity of different strains of mice to morphine can vary up to 20-fold.[41,94] Thus, each patient must be titrated individually, slowly increasing the dose and adjusting the dosing interval until pain relief is obtained. Keep in mind that patients may obtain better pain relief with one opioid than another and it is not possible to predict which drug is best for an individual patient.[95] Lower doses of medicine are needed to maintain pain relief than to take it away. Thus, administering analgesics regularly often leads to better pain control than giving the drug “as needed” (i.e., PRN). However, administration of opioids around-the-clock should be done only after establishing the optimal daily dose by titration since this approach can lead to progressive accumulation of drug, particularly longer-acting agents. [It typically takes approximately 5 halflives of the drug to reach steady-state levels.] For the patient’s comfort, try to use oral agents, remembering that oral doses may be higher than parenteral ones due to metabolism (i.e., “first-pass” effect) and their pharmacokinetics.



Table 11–4 General Guidelines in the Use of Opioids
• Respect individual differences among patients ◦ Doses and duration of action may vary from patient to patient • Dose titration is the rule and not the exception ◦ Slowly increase the dose until pain relief or limiting side effects occur • Administer opioids around-the-clock not as needed after optimal dose is established by dose titration • Remember equianalgesic dose ratios of drugs change when comparing naïve and tolerant patients • Anticipate and treat side effects ◦ Constipation: daily bowel regimen ◦ Sedation: decrease dose and increase frequency ◦ Nausea and vomiting: use antiemetics and/or switch drugs • Anticipate tolerance ◦ Increase dose appropriately ◦ Consider opioid rotation if further dose escalation is not possible ◦ Use adjuvant analgesics



Opiates have a number of side effects that should be anticipated and treated symptomatically if they occur, including s edation, constipation, nausea, vomiting, and respiratory depression.[96] Laxatives with stool softeners (e.g., sodium sulfosuccinate) are particularly important in view of the high rate of constipation. Sedation is best treated by avoiding high peak levels of drug by reducing the dose and increasing the frequency of administration. In select patients where sedation is particularly problematic, some clinicians will use dextroamphetamine or other stimulants. Nausea and vomiting may be treated symptomatically by administering antiemetics or by switching to another opiate. Indeed, it is not uncommon for patients experiencing high levels of nausea/vomiting with one drug to be able to take a different one without problem.

Oral Agents

Choosing an opioid analgesic can be confusing, with a large number available clinically (Table 11–5). Morphine is the standard against which all opiates are compared and all physicians should be familiar with its use. In large populations, all narcotics provide similar qualities of analgesia, and as a class, they have similar qualities and frequency of side effects as well. However, different patients may display widely varying levels of pain relief or side-effects to various drugs. Thus, choosing a drug is often empirical and if one agent is ineffective, another should be tried. Mild-to-moderate pain is best treated by oral medications, and most physicians initiate treatment with a combination product comprised with an opioid and either acetaminophen or an NSAID. Escalating the dosage of the combination products can be problematic due to the nonopioid medication and most clinicians will move to opioid-only formulations.

Table 11–5 Common Opioids
Immediate-release (IR) single-entity products Codeine Hydromorphone Methadone Morphine Oral Transmucosal Fentanyl Oxycodone Propoxyphene Levorphanol
Immediate-release combination products Codeine/acetaminophen Hydrocodone/acetaminophen Hydrocodone/ibuprofen Oxycodone/acetaminophen Oxycodone/aspirin Tramadol/acetaminophen
Sustained-release (SR) products Fentanyl Transdermal System Morphine Oxycodone Tramadol Oxymorphone

The duration of action of opioids can vary from minutes to days. The very short-acting compounds last only a few minutes are used almost exclusively during anesthesia. Of the more commonly used analgesics, methadone and levorphanol have much longer durations of action than most other opioids, enabling less frequent dosing. Titrating these agents, particularly methadone, can be difficult due to accumulation over time due to their extended elimination half-lives (18 to 24 and 24 to 36 hours, respectively) relative than morphine (2 to 3 hours).

In recent years, a wide range of extended release formulations have become available for a number of opioids. The choice of whether to use an immediate release (i.e., short acting) opioid or a long-acting one is not always simple. Most clinicians will recomment initiating therapy with a short-acting drug to determine its effectiveness in the individual patient. The short-acting drugs also can be titrated more rapidly. Once the patient is relatively stable, the daily dose of the short-acting agent can be converted to a similar dose of the extended release. Further titration should be done with the immediate release formulations and after determining the daily amount needed, it can be converted to the extended release formation.

The choice of short-acting and long-acting drugs also is dependent upon the pain. Many patients have a baseline, constant type of pain, which is particularly suited to the long-acting agents. However, patients with widely varying levels of pain through the day may be better managed by the shorter-acting drugs since they can be more easily adjusted throughout the day.

Certain drugs should be used cautiously. Meperidine is demethylated to normeperidine, a toxic metabolite that can accumulate and produce tremors, seizures, and myoclonus.[97] Patients with renal failure are particularly vulnerable since normeperidine is eliminated by the kidney. Mixed agonist/antagonists, such as pentazocine, can induce withdrawal in highly tolerant patients, since tolerant/dependent patients are highly sensitive to the antagonists. Addicts often report that they are allergic to these medicines. Finally, in past years heroin was widely used to treat pain in the United Kingdom as part of the so-called Brompton's cocktail. Although heroin is a potent analgesic and may have some advantages in selected patients, in large populations it shows few advantages over morphine.[98] Heroin is not available in the United States.

When facing limiting side effects, try switching the opiates. Patients often experience more side-effects with one drug than another. Rotating the opioids also may provide better pain relief due to incomplete cross-tolerance.

Intravenous Infusion

Administration of opioids by routes other than oral ingestion may be necessary when this route is impractical. Clinically important differences in drug effects may occur as a result of changes in route of administration and these alternative routes should only be initiated by clinicans experienced in their use. Continuous intravenous infusion of opioids is indicated when (1) patients require parenteral injections more frequently than every 3 hours, (2) patients experience prominent bolus effects such as sedation and rapid return of pain corresponding to peak and trough drug levels, or (3) rapid titration of drug doses is required to produce rapid pain relief. This mode of drug administration has become increasingly common in the management of postoperative and cancer pain. In the management of postoperative pain, morphine requirements during a 72-hour period in patients receiving intramuscular doses on a "as needed" (i.e., PRN) basis were far less drug than a comparable group receiving continuous infusions. Continuous infusions now typically are a feature of patient controlled analgesia (PCA). Here, infusions are maintained, but the patient has the opportunity to initiate a bolus of drugs at physician-defined doses and intervals. This approach has a number of significant advantages and is preferred by most patients. The patient has a sense of control and is less dependent on a busy nursing staff. The knowledge that he or she can easily obtain medication when needed eliminates a lot of anxiety, and studies indicate that patients using PCA actually require far less medication then when they use traditional dosing regimens. Incident pain, in which pain is associated with movement, is often quite difficult to treat. In theory, PCA may have the advantage in that patients can anticipate movement and "premedicate" themselves.

Subcutaneous Infusion

Subcutaneous infusion obviates the need for intravenous access and allows long-term parenteral administration of opioids outside the hospital.[99] In hospitalized patients, continuous subcutaneous infusion frees patients from delays in obtaining medication from the nursing staff, and patients can be discharged without compromising pain management. In addition, there has been the suggestion that continuous subcutaneous infusion is associated with fewer adverse side effects, particularly constipation, in comparison to intramuscular dosing.

Any opioid may be infused subcutaneously, although it is perhaps best to use short half-life, highly soluble drugs such as morphine or hydromorphone to avoid drug accumulation over time. Meperidine should be avoided due to the toxicity of its metabolite normeperidine, as noted earlier. In summary, the safety, efficacy, and ease of use of continuous subcutaneous infusions, even in the home, make this route of administration an attractive alternative for many patients in whom prolonged parenteral narcotic administration is required.

Spinal Epidural and Intrathecal Administration

Spinal epidural or intrathecal (subarachnoid) opioids have the advantage of providing prolonged durations of pain relief with fewer side effects.[100] Drugs can be administered intermittently through reservoirs or by continuous infusion through implantable and external pumps. This route is commonly used for management of obstetric analgesia, postoperative pain, and in cancer patients with bilateral or mid-line opioid-responsive pain below the level of the umbilicus, in whom adequate pain relief cannot be obtained with systemic opioids because of dose-limiting side effects.

Epidural or intrathecal administration produces cerebrospinal fluid morphine concentrations 10 to 100 times greater than those obtained with systemic administration[101–103] and also is associated with significant levels of drug in plasma, explaining the occurrence of unwanted supraspinal effects such as nausea and vomiting, pruritus, sedation, and respiratory depression. Factors that predispose to respiratory depression in postoperative pain management with spinal opioids include old age, use of large doses of hydrophilic opioids (e.g., morphine), lack of systemic opioid tolerance, and rapid changes in intrathoracic pressures such as might occur with positive end-expiratory ventilation. Urinary retention is also seen in up to 30% of patients, but this may be related to a spinal effect of morphine.

Adjuvant Analgesics

A number of other drugs are useful in the management of pain, either alone or in conjunction with opioid or nonopioid analgesics (Table 11–6).[104] Their use is particularly important in neuropathic pain and, in some neuropathic pain syndromes, they are the drug of choice.

Table 11–6 Nonopioids Used in Pain Management
Muscle relaxants
Baclofen
Carisoprodol
Chlorzoxazone
Cyclobenzaprine HCl
Orphenadrine citrate
Tizanidine
Anticonvulsants
Gabapentin
Pregabalin
Topiramate
Carbamazepine
Antidepressants[1]
Amitriptyline
Duloxetine
Nortriptyline
Venlafaxine



Anticonvulsants

This category of drugs can be particularly useful for the management of pain in chronic neuralgias such as trigeminal neuralgia, postherpetic neuralgia, glossopharyngeal neuralgia, and posttraumatic neuralgias. Carbamazepine is the drug of choice for management of trigeminal neuralgia, a syndrome that produces a paroxysmal, shooting, electric shock-like pain in a facial distribution. In recent years, gabapentin has become very widely used, and more recently pregabalin. It is generally less useful in managing the burning and aching sensations associated with neuropathic pain.

Phenothiazines

Methotrimeprazine is a potent analgesic equivalent in activity to morphine despite the fact that it does not interact with opioid receptors and its analgesia is insensitive to reversal by naloxone, indicating a nonopioid mechanism of action. It can be useful in the treatment of opioid-tolerant patients and helps to avoid the constipating and respiratory depressant effects of those drugs, but sedation and orthostatic hypotension are limiting side effects. Fluphenazine has been used as an adjuvant analgesic, particularly in combination with tricyclic antidepressants, in the management of painful neuropathies such as diabetic sensory neuropathy and postherpetic neuralgia.[105] A number of other phenothiazines are also useful in treating opiate-induced emesis, but they may exacerbate sedative effects. Their chronic use should be limited because of the possibility of tardive dyskinesias.

Antidepressants

These agents possess direct analgesic effects in animal models[106] and are the drugs of choice for a number of chronic pain syndromes, neuropathic pains, and migraine.[104] Their mechanisms of action are still not clear, but may be related to their blockade of serotonin and norepinephrine uptake. Amitriptyline has the best-documented analgesic actions,[107] but its anticholinergic actions, such as dry mouth, orthostatic hypotension, and, rarely, urinary retention or delirium, can interfere with its use. It is generally administered once a day and at doses far lower than those used to treat depression. Should side effects interfere with therapy, switching to an alternative antidepressant can be helpful. The choice of agent is empirical. They are often used in conjunction with opiates, where there is evidence in preclinical studies that they enhance analgesia.

Dextroamphetamine

Amphetamines also enhance opioid analgesia when combined with opiates in the postoperative period,[108] but are rarely used. Dextroamphetamine is more commonly employed to reduce the sedative effects of opioids, though even this use is uncommon.

Steroids

Prednisone, hydrocortisone, and dexamethasone have specific and nonspecific effects in pain management. They are the drugs of choice for temporal arteritis and polymyalgia rheumatica and may prove useful in intractable migraine or cluster headaches. They may be oncolytic for some tumors (e.g., lymphoma) and may ameliorate painful nerve or spinal cord compression or bone metastases by reducing edema in tumor and nervous tissue, with a concomitant decrease in pain. They are used in the treatment of spinal cord compression and they often can markedly relieve the pain. Their use is usually based on the underlying disease, however, and they are not often prescribed specifically for pain. They retain their typical side effects, some of which may prove helpful, such as an increase in appetite and euphoria. Others, including the propensity to cause gastrointestinal bleeding, proximal myopathy, and (rarely) psychosis, may prove troublesome. Rapid withdrawal of steroids may exacerbate pain independent of the progression of systemic cancer (pseudorheumatoid syndrome).[109]

Antihistamines

Hydroxyzine has analgesic and antiemetic activity in addition to its antihistamine effects. It may produce additive analgesia when combined with opioids, with only slightly more sedation, so that it is a useful adjuvant for the anxious, nauseated patient. However, it is not commonly used.

Agents to Be Avoided in the Pharmacologic Management of Pain

Benzodiazepines are effective for treatment of acute anxiety attacks and muscle spasm, but do not have analgesic properties. Their routine use is not recommended for the treatment of chronic pain. Although acute pain is often associated with typical signs of anxiety, treatment should focus on the cause of pain and the use of specific analgesic agents.

Barbiturates and other sedative-hypnotic drugs also lack intrinsic analgesic properties and should generally be avoided in the management of pain. Many commonly used analgesics are formulated in combination with barbiturates and must be prescribed with caution. Although delta-9-tetrahydrocannabinol has some analgesic properties in controlled clinical studies, it is associated with high incidence of dysphoria, drowsiness, hypotension, and bradycardia. Its routine use cannot be recommended for management of pain in cancer, although it does have some efficacy as an antiemetic for chemotherapy-induced nausea and vomiting. Although a synthetic cannabionoid, nabilone, is currently available, it is not widely used for pain.

Finally, cocaine has local anesthetic properties, but controlled trials have demonstrated no efficacy as an analgesic alone or in combination with opiates.

Placebo Response

The placebo response is common. Thus, testing patients with saline to see if their pain is real provides no useful information. In fact, many patients with a documented organic basis for their pain will obtain a temporary response when given a placebo. The deceptive use of placebos to distinguish psychogenic from real pain should be avoided.

Pain in Children

Children may have acute or chronic pain, but inadequate verbal skills and/or their misconceptions about the etiology or consequence of pain may alter the symptoms and signs. Children should receive opioid analgesics when confronted with surgical procedures and/or painful complications of disease, such as that accompanying cancer. Assessing pain in young children can be difficult. As in adults, autonomic signs may not be present in chronic pain. Young children may refuse to take oral medication or intermittent injections and in this situation the intravenous route is used.

The dosage of the medication varies with age, as with many drugs. As with adult, children may need titration to achieve adequate pain control. There is no evidence to suggest that preadolescent or adolescent children are at a higher risk for addiction than the general population when opiates are administered for pain. Like adults, they will develop tolerance with chronic therapy and may require larger doses to adequately control their pain, particularly with advanced cancer.

Analgesics in the Elderly

Analgesics may be given safely to geriatric patients, although adjustments of doses are usually required. The elderly are usually more sensitive to opiates such as morphine and starting doses are generally smaller. In addition, patients with CNS disease or renal disease may be more sensitive to opiates. Elderly patients are also more sensitive to the actions of the tricyclic antidepressants and therapy is usually initiated at very low doses. The tricyclics must be used cautiously in older men with prostatic hypertrophy

due to their predisposition toward urinary retention, as well as in patients with cardiac conduction problems.

Conclusion

Advances in understanding the neuropharmacology and neurophysiology of pain have provided a more rational basis for its treatment. Pain can be classified according to its source into somatic, visceral, and deafferentation types. The three types of pain are mediated by distinct networks of neuron receptors and neuroanatomic pathways. Deafferentation pain from nerve damage typically has a very unpleasant, burning quality that distinguishes it from somatic or visceral pain. Different classes of pain often are best treated with different drugs and may require different doses of those drugs. Neuropathic is particularly difficult to treat and often is treated with anticonvulsants and antidepressants. Although neuropathic pain is sensitive to opioids, it may require higher than normal opioid doses. It is also useful to classify pain as either acute (less than six months duration) or chronic.

Mild-to-moderate pain is often best treated by NSAIDs, many of which are available over the counter. However, these agents often present significant side-effects, particularly with regards to GI symptoms. The COX-2 selective agent celecoxib avoids some of these issues. Their use is also limited by their ceiling effect, making their use alone for severe pain difficult. However, there is evidence that some of these agents may interact synergistically with opioids,[110,111] expanding their role in the management of more severe pain.

Opioid analgesics are the most effective class of drugs for treatment of moderate or severe visceral and somatic pain. Addiction to opiates rarely develops during the treatment of acute pain, although clinicians need to be vigilant with chronic dosing of these drugs. Opioids activate the brain's own opioid antinociceptive system composed of neuropeptides (i.e., enkephalins, dynorphins, and endorphins) and specific opioid receptors. The drugs act at one or more subtypes of opioid receptors that are distributed at different levels of the nervous system and mediate distinct actions. The first opiate receptor to be discovered, the mu receptor, mediates actions of morphine. In recent years a host of mu receptor variants generated from the same gene have been identified, possibly explaining many of the clinical observations of the mu opioids. Switching from one opioid to another in tolerant patients may restore analgesia, an approach termed *opioid rotation*. Differences in route of administration or duration of action may also be important determinants influencing the choice of drug. Adjuvant drugs, not usually thought of as analgesics, may relieve pain in combination with other drugs or alone. This group includes anticonvulsants, phenothiazines, antidepressants, steroids, and antihistamines.

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Neurologic Metabolic Diseases

Chapter: Neurologic Metabolic Diseases
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An inborn metabolic disease is a quantitative or qualitative defect in a biochemical reaction. Most metabolic diseases are due to enzyme dysfunction, and others are due to defective transport molecules. There are several hundred inborn metabolic diseases. Many of these diseases cause a neurologic phenotype. Instead of an encyclopedic review of the treatment of all neurologic metabolic diseases, this chapter includes a selection of prototypic inborn metabolic diseases and their treatment. Emphasis in placed on treatable conditions that are relatively common or that should be routinely considered in the evaluation of children with an undiagnosed neurologic disease.

Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is an X-linked disorder due to deficiency of a peroxisomal membrane protein, ALDP. ALDP transports very-long-chain fatty acids across the membrane, and deficiency of the transporter leads to impaired oxidation of very-long-chain fatty acids. The transporter is a monomer encoded by the gene *ABCD1* at Xq28. Adrenoleuko dystrophy is the most common peroxisomal disorder. It causes four different phenotypes: (1) childhood cerebral form, (2) adrenomyelo neuropathy, (3) isolated primary adrenocortical insufficiency, and (4) asymptomatic status.[1] The childhood cerebral form is the most common presentation. It presents in boys during the second half of the first decade of life with behavioral changes such as attention-deficit problems and school failure. They develop progressive hearing loss, vision loss, spasticity, and ataxia, and they typically succumb in a period of years. Adrenal insufficiency causes episodes of hypoglycemia and salt wasting as well as progressive hyperpigmentation of the skin. Adrenomyeloneuropathy causes progressive spastic paraparesis without adrenal insufficiency in both adult men and women. It is rarely fatal.

Laboratory findings in adrenoleukodystrophy include elevated plasma very-long-chain fatty acids, including C26, C25, and C24. The levels of C22 and C20 are within normal limits. The ratio of C26:C22 is markedly elevated, and this ratio can be quite useful in diagnosing this disease.[2] Brain magnetic resonance imaging (MRI) reveals bilateral and symmetric increased white matter signal in the posterior and occipital lobes. Inflammation at the edge of the white matter lesion causes a ribbon of enhancement on contrast studies. Adrenomyeloneuropathy is also associated with elevated very-long-chain fatty acids. Men with this condition may show progressive white matter changes.

There is no treatment that can stop the progression of symptoms of adrenoleukodystrophy in individuals who are already manifesting neurologic impairment,[3] but symptomatic treatment should be provided. Bone marrow transplantation is efficacious when it is performed early in the course of the illness when neurologic or neuropsychiatric manifestations are absent or minimal.[4] Moser and colleagues studied the efficacy of Lorenzo's oil in presymptomatic boys with ALD.[5] In their single-arm clinical study the reduction of hexaconsanoic acid with Lorenzo's oil was associated with reduced risk of developing MRI abnormalities in those boys whose initial MRI was normal. Thus,

treatment with Lorenzo's oil and bone marrow transplantation are effective, but they must be initiated before neurologic symptoms occur. This is usually only feasible when another affected individual in the family has been previously diagnosed. Thus, plasma very-long-chain fatty acid analysis should be performed on all presymptomatic first-degree relatives of an affected proband.

Since the progression of symptoms is slower in adrenomyeloneuropathy, symptomatic treatment of spasticity is the mainstay of therapy. However, the efficacy of bone marrow transplantation has also been studied for this phenotype. Hitomi et al performed a bone marrow transplant in a 20-year old man with adult-onset progressive right hemiparesis, gait disturbance, mild cognitive impairment, and increased signal of the left corticospinal tract on MRI.[6] Though the authors report that this as a case of adult-onset ALD the presentation is consistent with adrenomyeloneuropathy. Over a two-year period the affected individual's motor function return to nearly normal, and the white matter abnormalities improved but did not normalize.

Biotinidase deficiency

Biotinidase deficiency is an autosomal recessive condition due to mutations in the *BTD* gene on chromosome 3. Biotin is an essential vitamin cofactor for at least four carboxylase enzymes: propionyl-CoA carboxylase, pyruvate carboxylase, 3-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase. Biotinidase cleaves biocytin to form biotin and lysine. Therefore, a deficiency of this enzyme causes impaired function of the carboxylase enzymes because they lack the cofactor. Infantile epilepsy, including myoclonic seizures, generalized seizures or infantile spasms, is the classic feature of biotinidase deficiency. If untreated, other neurologic features can develop, including ataxia, hypotonia, developmental delay, optic atrophy, sensorineural hearing loss, and psychomotor regression. Dermatologic abnormalities are also quite common in this disorder, including desquamation, perioral stomatitis, glossitis, and alopecia.

Individuals may develop acute ketoacidotic episodes like those seen in propionic acidemia, while others may have only chronic lactic acidosis. Acute episodes may also be associated with hyperammonemia. Most individuals with biotinidase deficiency have characteristic abnormalities on organic acid analysis, including elevations of 3-hydroxypropionic acid (deficiency of propionyl-CoA carboxylase), 2-methylcitric acid (deficiency of propionyl-CoA carboxylase), tiglyglycine (deficiency of propionyl-CoA carboxylase), 3-hydroxyisovaleric acid (deficiency of 3-methylcrotonyl-CoA carboxylase), and 3-methylcrotonylglycine (deficiency of 3-methylcrotonyl-CoA carboxylase). Biotinidase activity in the serum is included in many newborn screening programs throughout the world.

Treatment with biotin 10 mg/day is extremely effective.[7] All biochemical abnormalities resolve, the seizures promptly cease, and the dermatologic problems abate. There are no side effects of the medication. However, ifthe diagnosis and treatment are delayed, affected individuals may have irreversible hearing loss, vision loss, mental retardation, and ataxia.[8] Given the dramatic improvement of biotin supplementation in individuals with biotinidase, this disorder should be considered in any infant or young child with an undiagnosed epilepsy syndrome. Initiation of treatment in the newborn period following diagnosis through newborn screening should prevent the development of any manifestations of this metabolic disease.

Congenital disorders of glycosylation

Formerly called carbohydrate-deficiency glycoprotein syndromes, congenital disorders of glycosylation (CDGs) comprise a group of several disorders that are secondary to impaired N-glycosylation or O-glycosylation of glycoproteins. Proper function of most proteins requires that an oligosaccharide chain (called a glycan) is attached to the amide (N-glycosylation) or hydroxyl group (O-glycosylation) of the protein. N-glycosylation requires three steps: formation of the oligosaccharide sugar, attachment of the sugar onto the protein, and processing of complex by pruning the oligosaccharide moiety once it is attached to the protein. N-glycosylation disorders are divided into two groups: group I comprises 13 disorders (CDGIa to CDGIL) in the formation of the oligosaccharide glycan due to autosomal recessive enzyme defects, and group II comprise six autosomal recessive disorders (CDGIIa to CDGIIf) in the processing of the glycan once it is attached to the protein. O-glycosylation disorders include Walker-Warburg syndrome, Muscle-Eye-Brain disease, and multiple exostoses syndrome. Disorders of O-glycosylation will not be discussed further in this chapter.

Given the numerous subtypes of CDGs that exist, it should be no surprise that this category of diseases has protean manifestations. For example, CDGIa, the most common CDG, typically causes mental retardation, hypotonia, strabismus, ataxia, hyporeflexia, and dysmorphic facial features. Other features may include epilepsy, stroke-like episodes believed to be secondary to decreased levels of antithrombin III and other coagulation inhibitors,[9] failure to thrive, hepatomegaly, retinitis pigmentosa, inverted nipples, cardiomyopathy, recurrent episodes of pericardial effusion, hypogonadism, and skeletal anomalies. Classically, pontocerebellar hypoplasia or atrophy is evident on brain MRI imaging. There is also usually evidence of liver dysfunction, including elevated serum liver transaminase levels, high cholesterol, and low albumin. Proteinuria has also been reported.

Unlike CDGIa, CDGIIe causes loose and redundant skin, abnormal ears, a short neck, abnormal development of the humeral and tibial epiphyses, hepatosplenomegaly, progressive jaundice, and recurrent infections and cardiac insufficiency that can lead to death in early infancy.[10] Similar to CDGIa, the two siblings who have been reported with this disease also had epilepsy and generalized hypotonia. Additional clinical features that have been reported in other CDGs include dry skin, colobomas, fetal hydrops, and elevated creatinine kinase levels. Given the broad clinical spectrum of this category of diseases, Jaeken recommends testing for these disorders in any individual who has any unexplained clinical condition.[11]

Although there are several subtypes of CDGs, diagnosis begins with a single screening test, isoelectric focusing of serum transferrin. It is important to note that this is a screening test because it will identify most, but not all, forms of CDG. It only identifies those CDGs that cause abnormal N-glycosylation associated with sialic acid deficiency. Confirmation of the diagnosis of a specific CDG requires measuring the activity of specific enzymes in fibroblasts. The pattern of abnormal isoelectric focusing (abnormal assembly versus abnormal processing) can help guide the selection of the specific enzyme assays that are performed.

At this time CDGIb is the only treatable CDG. It is also the only known CDG that does not cause neurologic problems. CDGIb predominantly causes hepatic and gastrointestinal symptoms, including liver disease, hypoglycemia, recurrent vomiting, feeding problems, abdominal pain, and protein-losing enteropathy. Coagulopathies may also occur. Neurologic manifestations are very uncommon, and they are minor when they do occur. Cognition is typically preserved. There are no distinctive dysmorphic features. CDG1b is an autosomal recessive processing defect of the oligosaccharide chain due to phosphomannose isomerase enzyme deficiency. This enzyme catalyzes the conversion of fructose-6-phosphate to mannose-6-phosphate. This is the first step in the synthesis of GDP-mannose, one of the oligosaccharide chains. The treatment for this condition is mannose, though the recommended dose varies from 1 gram/kg per day divided into doses[12] to 100–300 mg/kg/day divided into 4–6 doses.[13] Osmotic diarrhea is a potential side effect of mannose therapy. A different hexokinase enzyme converts mannose to mannose-6-phosphate, thus bypassing the enzymatic defect. Typically, the clinical symptoms disappear once the treatment is initiated. Though treatment for CDGIb is highly successful, there is no effective treatment for the CDGs that cause neurologic abnormalities.

Creatine deficiency syndromes

There are three distinct genetic conditions that comprise the creatine deficiency syndromes: arginine: glycine amidinotransferase (AGAT) deficiency, guanidinoacetate methyltransferase (GAMT) deficiency, and the creatine transporter defect. Arginine:glycine amidinotransferase in the pancreas and kidney catalyzes the synthesis of guanidinoacetate (GAA) from arginine and glycine, the first step in the metabolism of creatine. Deficiency of this enzyme due to mutations in the *AGAT* gene on chromosome 19 causes mental retardation, speech delay, and seizures. Next, guanidinoacetate methyltransferase in the liver catalyzes the methylation of GAA to form creatine. Deficiency of this enzyme due to mutation in the *GAMT* gene on chromosome 15 leads to developmental arrest, mental retardation, seizures, and extrapyramidal movement disorders. Creatine is transported into the muscle and brain via a sodiumdependent and chloride-dependent creatine transporter. Deficiency of this enzyme due to mutations in *SLC6A8* gene on the X chromosome causes mental retardation, speech delay, seizures, hypotonia, and microcephaly that may be associated with brain atrophy in boys. Girls with a single mutation may be asymptomatic, have learning disabilities or behavioral problems, or show severe cognitive impairment, depending on the pattern of X-inactivation.

Diagnosis of these diseases begins with quantification of the urinary levels of GAA and the urinary creatine/creatinine ratio. In AGAT deficiency, both GAA and the creatine/creatinine ratio are low. In GAMT deficiency, the GAA level is high, and the creatine/creatinine ratio is low. In boys with the creatine transporter defect, the creatine/creatinine ratio is high because creatine is not reabsorbed once it is filtered. Due to variable X-inactivation, urinary studies are not adequate to rule out the presence of a creatine transporter defect in girls. For all of these disorders, a low or absent creatine peak on brain magnetic resonance spectroscopy will identify all individuals with a creatine deficiency syndrome. In GAMT deficiency there may be bilateral and symmetric increased signal abnormalities in the globus pallidus.

Creatine supplementation and arginine restriction are the mainstays of treatment for GAMT deficiency. Creatine supplementation of 300–400 mg/kg/day in 3–6 divided doses improves seizure control, decreases extrapyramidal movements, and may improve the developmental outcome.[14,15] Arginine restriction may also provide additional benefit.[14] Carnitine supplementation has been used in individuals with AGAT deficiency,[16] but its efficacy is still undetermined since only a few patients with this defect have been reported. Oral creatine therapy is not effective for treating the neurologic manifestations of the creatine transporter defects. For all patients with these disorders, symptomatic treatment of epilepsy and any movement disorder is warranted.

Fabry disease

Fabry disease is an X-linked disorder due to α-galactosidase deficiency. This lysosomal enzyme cleaves the terminal galactose from a glycosphingolipid, ceramide trihexoside. Glycosphingolipids accumulate in the lysosomes of many cells, but the pathogenesis of this disease is predominantly due to accumulation in endothelial cells within small vessels. Untreated, Fabry disease typically presents with a painful neuropathy of the hands and feet. Dermatologic features include angiokeratomas and hypohydrosis. Individuals with Fabry can have diarrhea. Ophthalmologic abnormalities include cataracts of the posterior lens and corneal opacities. Severe long-term sequelae include chronic renal disease associated with proteinuria and hypertension, strokes, and cardiovascular manifestations, such as myocardial infarction, cardiomegaly, and dysrhythmias. Though the disease is X-linked, symptoms can develop in both men and women.

Fabry disease is treated with enzyme replacement therapy and symptomatic management. Enzyme replacement with agalsidase-α (Fabrazyme) or agalsidase-β (Replagal) can be used to treat Fabry disease, but only Fabrazyme is approved in the US. In a study of the safety and efficacy of agalsidase-α in 58 patients, a five-week course of the medication showed a marked decrease in the accumulation of ceramide trihexoside in the endothelial cells of the kidney, heart, and skin.[17] The medication dose is 1 mg/kg. It is given by intravenous infusion every two weeks. The infusion rate begins at 0.25 mg/min (15 mg/h) and can be increased in increments of 0.05 to 0.08 mg/min up to a total of about 33 mg/h. The most common side effect from the medication is an acute infusion reaction. Symptoms of this reaction may include rash, tachycardia, hypertension, chest pain, dyspnea, fever and chills, abdominal pain, urticaria, pruritus, nausea, vomiting, edema, hypotension, myalgia, and headache. Most individuals receiving the enzyme infusion also develop IgG antibodies to the synthetic enzyme.

Symptomatic treatment is usually also necessary in individuals with Fabry disease, even in those receiving the enzyme replacement therapy. Neuropathic pain can be treated with carbamazepine, phenytoin, gabapentin, topiramate, and other pain medications. Chronic hemodialysis is required if renal failure develops, and many patients require kidney transplantation.

Glucose transporter deficiency syndrome

Glucose transporter deficiency syndrome is due to impaired function of GLUT1, a transmembrane protein that transports glucose into the

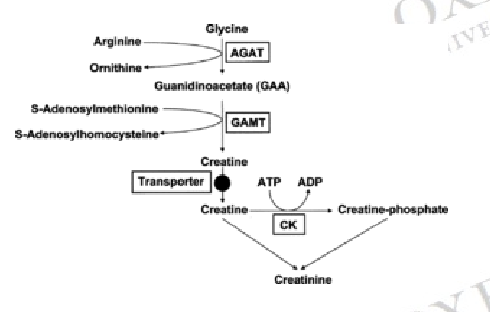


Figure 12–1.
Creatine metabolism.

brain across the blood-brain barrier. This disorder is due to mutations in the *GLUT1* gene on chromosome 1. Most cases are autosomal recessive, but autosomal dominant inheritance has been rarely reported.[18] The classic presentation is severe epilepsy within the first year of life following an uncomplicated pregnancy and delivery. A variety of seizures may develop, including tonic-clonic, myoclonic, absence, and atonic seizures. Other associated neurologic problems include global developmental delay, hypotonia that may progress to spasticity, dystonia, ataxia, and acquired microcephaly. The only laboratory abnormality is hypoglycorrhachia. It is best to compare the CSF glucose to blood glucose, and a ratio of <0.46 is diagnostic.[19] The brain MRI is normal.

During fasting ketones are the primary energy source for the brain. In individuals with glucose transporter deficiency syndrome, the ketogenic diet can be used to provide a constant source of ketones as an energy source for the brain. The ketogenic diet is a high-fat, low protein diet that is used throughout childhood and adolescence in individuals with this deficiency. Individuals frequently have complete seizure control, and additional anticonvulsant therapy may not be necessary.[19] Furthermore, chronic use of the ketogenic diet can improve developmental outcomes and decrease the severity of movement disorders. It has been suggested that medications that impair GLUT1 function should be avoided, including diazepam, phenobarbital, caffeine and alcohol.[20]

Glutaric aciduria type i

Glutaric aciduria type I is an autosomal recessive condition due to deficiency of the enzyme glutaryl-CoA dehydrogenase. This single enzyme catabolizes lysine, hydroxylysine, and tryptophan through two sequential reactions: the conversion of glutaryl-CoA to glutaconyl-CoA and the subsequent conversion of glutaconylCoA to crotonyl-CoA. The enzyme is composed of a single subunit that is encoded by the *GCDH* gene on chromosome 19. Glutaric aciduria type I causes a variety of clinical problems. Megencephaly may be present at birth or may develop in the first months of life. Some infants may have nonspecific signs and symptoms, such as jitteriness, vomiting, and hypotonia. Most affected individuals then develop an acute decompensation in which there is a profound loss of developmental skills. This decompensation may cause irreversible neurologic manifestations, including developmental delay, choreoathetosis or dystonia due to basal ganglia infarcts, epilepsy, and severe hypotonia. Some children have recurrent decompensations that are associated with progressive loss of neurologic function. Others may have only a single decompensation. Finally, a minority of patients has an insidious loss of neurologic function without acute decompensations. Cognitive function is preserved initially, but repeated neurologic damage causes cognitive dysfunction. Other possible features include sweating, recurrent episodes of fever, and hepatomegaly. Retinal hemorrhages may occur, leading many clinicians to appropriately consider nonaccidental trauma in the differential.

The neurologic decompensations are not typically associated with severe laboratory abnormalities. Mild acidosis may be present. In rare cases there may be ketosis,

hyperammonemia, hypoglycemia, and elevated liver transaminase levels in the serum. Organic acid analysis typically reveals enormous quantities of glutaric acid as well as marked elevations of 3-hydroxy-glutaric acid and glutaconic acid. Glutarylcarnitine is elevated in the acylcarnitine profile, and this disorder can be detected in newborns when the acylcarnitine profile is part of the newborn screening program. Brain MRI findings include perisylvian atrophy, white matter changes, and increased signal intensity in the basal ganglia, especially the striatum. Subdural hematomas may also be present.

Treatment for acute decompensations is similar to the management of other inborn metabolic diseases that cause acute metabolic derangements. Adequate caloric intake from glucose should be provided using 10% dextrose solution or higher, protein should be avoided, and carnitine supplementation is required.[21] Chronic treatment includes dietary restriction of lysine using a lysine-free amino acid formula. Tryptophan intake in the diet may simply be minimized. Carnitine should be prescribed at 50–100 mg/kg/day. Hoffmann and Zachocke have suggested that this treatment can prevent acute decompensations and progressive neurologic deterioration in up to 90% of affected individuals, while lack of treatment leads to severe neurologic impairment in over 90% of affected individuals.[22] Symptomatic treatment with antispasmodic and anticholinergic agents may be warranted.

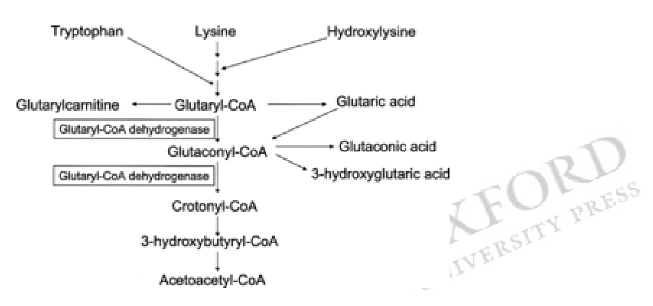


Figure 12–2.
Lysine metabolism and glutaric aciduria type I.

Homocystinuria

Homocystinuria is an autosomal recessive disorder due to cystathionine β-synthase deficiency. This enzyme catalyzes the conversion of homocysteine to cystathionine. Cobalamin and pyridoxine are cofactors of the enzyme. The enzyme is encoded by the *CBS* gene on chromosome 21. If untreated, this disease can cause strokes, global developmental delay and mental retardation, and epilepsy. Ophthalmologic abnormalities that can occur include ectopia lentis, myopia, glaucoma, and retinal detachment. Individuals with homocystinuria typically have a Marfanoid habitus with arachnodactyly, decreased joint mobility, pes cavus and pectus carinatum or pectus excavatum. In addition to strokes, renal artery and carotid artery thrombi as well as pulmonary embolism may occur.

Individuals with homocystinuria have elevated total homocysteine levels in plasma. On amino acid analysis in plasma, methionine and homocystine are elevated, and cystine is low. Other defects of methionine and tetrahydrofolate metabolism can cause elevated homocysteine levels, but they do not cause elevated methionine levels. Cobalamin disorders (except cobalamin A and cobalamin B) also cause elevations of homocysteine, but the methionine level is normal. Newborn screening programs screen for homocystinuria by detecting elevated methionine levels.

Approximately 50% of individuals with homocystinuria are responsive to pyridoxine. The response may be partial, but even a partial response will allow an individual to have a diet that is less restrictive for methionine. The starting dose of pyridoxine is 100 mg/day. It can be increased up to 500–1000 mg, but the dose in infants and children should be 250 mg/day or less.[23] To avoid secondary folate deficiency, supplemental folic acid (5–10 mg/day) should to be provided. The majority of individuals with homocystinuria must be placed on a methionine-restricted diet. A strict diet low in methionine is required for those who are unresponsive to pyridoxine. Betaine (approximately 150 mg/kg/ day) can also be used to lower the homocysteine level.[24] The efficacy of antithrombotic agents has not been proven. Yap and colleagues have shown that lower plasma homocysteine levels significantly reduce cardiovascular risk in individuals with homocystinuria.[25] Additionally, a single study has shown that vitamin C 1g/day for six months improved endothelial function,[26] suggesting that vitamin C supplementation may decrease the risk of thrombosis in individuals with homocystinuria.

Lesch-nyhan disease

Lesch-Nyhan disease is an X-linked disorder due to hypoxanthine guanine phosphoribosyl transferase (HPRT) enzyme deficiency in the salvage pathway of purine bases. This enzyme catalyzes the conversion of hypoxanthine or guanine to form their respective nucleotides, inosinic acid or guanylic acids. The enzyme is encoded by the gene *HPRT* on Xq26. One of the earliest manifestations of this disorder is orange crystals in the urine of infant boys, and these crystals can predispose to nephrolithiasis and hematuria. In the second half of the first year of life, the boys begin to demonstrate neurologic abnormalities, including lack of motor development and hypotonia. A variety of movement disorders invariably develops, including dystonia, choreoathetosis, and ballismus. All of the affected individuals also develop characteristic self-mutilatory behavior as well as aggressiveness. Progressive pyramidal features include spasticity, hyperreflexia, and opisthotonic spasms.

Hypoxanthine guanine phosphoribosyl transferase deficiency causes an accumulation of hypoxanthine. Xanthine oxidase converts hypoxanthine to xanthine, and xanthine to uric acid. Thus, marked elevations of uric acid in blood and urine are noted in almost all individuals with Lesch-Nyhan syndrome. Hypoxanthine, but not uric acid, is elevated in cerebrospinal fluid.[27] In addition to predisposing to crystalluria and hematuria, uric acid elevations can lead to renal insufficiency and gout in untreated individuals.

Treatment of Lesch-Nyhan syndrome includes allopurinol therapy to decrease uric acid levels and symptomatic management of the associated movement disorders and behavioral problems. Allopurinol at doses of 200–400 mg/ day completely prevents the sequelae of hyperuricemia. However, treatment is limited for the self-mutilatory behavior that is the most troubling symptom of this disease. There are no pharmacologic agents that provide long-term benefit for this behavior. Therefore, aggressive symptomatic treatment must be used, including a variety of oral appliances,[28] physical restraint, and selective teeth removal. Taira and colleagues reported that chronic stimulation of the globus pallidus internus completely abolished self-mutilation in a single patient.[29] Treatment of associated movement disorders may also be necessary.

Maple syrup urine disease

Maple syrup urine disease (MSUD) is an autosomal recessive disease due to branched-chain oxoacid dehydrogenase deficiency. This is the second enzymatic reaction in the catabolism of the branched chain amino acids—isoleucine, leucine, and valine. The oxoacid dehydrogenase is a multimeric complex of three subunits composed of four proteins. E1, a decarboxylase, is a tetramer of two proteins (α and β) in a $\alpha_2\beta_2$ structure. E1a is encoded by a gene on chromosome 19, and E1β is encoded by a gene on chromosome 6. The second subunit of the complex, E2, is an acyl transferase, and it is encoded by a gene on chromosome 1. The E3 subunit is a flavoprotein lipoamide dehydrogenase that is encoded by a gene on chromosome 7. After a brief asymptomatic period, infants with classic MSUD develop an acute onset of progressive and nonspecific symptoms and signs, including vomiting, poor feeding, lethargy, high-pitched cry, flaccidity that develops into hypertonia or rigidity, and seizures. If untreated, affected babies will manifest respiratory arrest, coma, and death. These symptoms and signs are due to worsening cerebral edema. Survivors will have irreversible brain injury, cerebral palsy, and mental retardation. A maple syrup smell may be noted, especially in cerumen. However, it is not always detected. As in other organic acidurias, recurrent episodes can be triggered by catabolic stress, such as infections or fasting. There is an increased incidence of pancreatitis in individuals with MSUD.

There is variable expressivity in the clinical phenotype of MSUD. For example, some individuals are responsive to thiamine, a cofactor for the enzyme complex. These individuals have residual enzyme function. Other individuals have intermittent MSUD and present with acute decompensations, but are entirely unaffected between episodes. In intermediate MSUD individuals rarely have acute decompensations, yet have mental retardation and biochemical and molecular evidence of MSUD. These distinctions are simply various manifestations of a spectrum of disease, and there is no useful correlation between residual enzyme function and the phenotype for these individuals.[30]

Most decompensations from MSUD are not associated with severe acidosis or other abnormalities on routine laboratory studies. Rarely, hypoglycemia or mild acidosis occurs. Ketonuria may also develop in an acute episode. As mentioned above, during an acute decompensation cerebral edema may be noted on neuroimaging studies. White matter changes may be noted at baseline. Marked elevations of leucine as well as isoleucine and valine can be detected on amino acid analysis in plasma. Alloisoleucine, a metabolite of leucine, is pathognomonic for MSUD. Organic acid analysis reveals elevations of the branched-chain 2-keto acids. In the newborn screening programs that use tandem mass spectroscopy, an elevation of a single peak of combined leucine and isoleucine can identify asymptomatic babies with MSUD.

Treatment for acute decompensations from MSUD is a medical emergency.[31,32] Catabolism must be stopped and anabolism established. Similar to other organic acidurias, this is best accomplished by providing normal saline boluses for dehydration, liberal fluid resuscitation with 10% glucose solution at one and one-half to twice the maintenance rate, cessation of protein intake, and 2 g/kg/day intralipid administration for caloric supplementation. Bicarbonate should be used carefully to correct severe acidosis. However, the provision of aggressive intravenous fluid hydration with generous caloric intake to prevent catabolism will frequently help correct a mild acidosis. Insulin may need to be started for hyperglycemia. For patients who do not have intractable vomiting, slow and continuous enteral administration of an amino acid mixture that does not include the branched-chain amino acids should be provided. Supplementation with alanine and glutamine is required. As the leucine level decreases, supplemental valine and isoleucine is required to avoid deficiencies of these amino acids and subsequent reinitiation of catabolism.

For newly diagnosed patients, responsiveness to thiamine should be measured. A chronic daily dose of thiamine should be given to any individual who is thiamine-responsive. For those who are not responsive to thiamine, chronic management of MSUD is challenging. It requires adherence to a tightly controlled diet that restricts branched-chain amino acid intake to the required amount for normal growth. A synthetic formula that lacks isoleucine, leucine, and valine is combined with a very low protein diet. Alanine and glutamine must frequently be supplemented into the formula. Liver transplantation has been performed in a handful of individuals with MSUD. They no longer required a protein-restricted diet, and there was no ongoing risk of metabolic decompensation.[33,34] Thus, this option seems reasonable in those individuals who have frequent or severe decompensations.

Methylmalonic aciduria syndromes

Methylmalonic acidemia (MMA) is a group of several autosomal recessive diseases due to methylmalonyl-CoA mutase deficiency or defects in the enzyme's cofactor, adenosylcobalamin. Methylmalonyl-CoA mutase follows propionylCoA carboxylase in the catabolism of valine, isoleucine, threonine, methionine, odd-chain fatty acids, and cholesterol. It converts methylmalonyl-CoA to succinyl-CoA, a compound in the Krebs cycle. This enzyme is encoded by the MUT gene on chromosome 6. Mutations that cause absence of all enzyme activity are called mut^0, and mutations that yield some residual enzyme function are called mut^-. Cobalamin A and cobalamin B disorders cause MMA secondary to defects in the synthesis of adenosylcobalamin, the cofactor for the mutase enzyme. Cobalamin A is due to mutations in the *MMAA* gene on chromosome 4, and cobalamin B is due to mutations in the *MMAB* gene on chromosome 12. Cobalamin C, D and F disorders cause MM A as well as homocystinuria because there is a defect in the synthesis of both adenosylcobalamin and methylcobalamin (cobalamin C and D) or in the transport of cobalamin from the lysosome into the cytoplasm (cobalamin F). Cobalamin C is encoded by the *MMACHC* gene on chromosome 1. Cobalamin D and cobalamin F have only been reported in a few patients, and the underlying genetic basis is currently unknown.

Individuals with MM A present with acute and recurrent metabolic decompensations that cause severe vomiting, lethargy that can progress to coma, cerebral edema, and brain injury or death, even if treated aggressively. These episodes can be triggered by any metabolic stress, including a protein load in the diet, infections, or prolonged fasting. Additional neurologic features may include infantile hypotonia that may evolve into hypertonia and spastic tetraparesis, global developmental delay and mental retardation, epilepsy, dystonia, basal ganglia strokes, and brain atrophy. Unlike individuals with propionic acidemia, individuals with MMA frequently develop renal disease, including renal tubular acidosis, hyperuricemia, and chronic renal failure. Other chronic problems include recurrent pancreatitis, skin lesions, and osteoporosis.

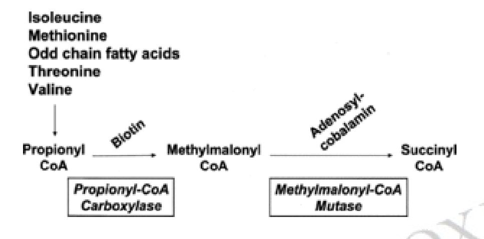


Figure 12–3.
Propionic acidemia and methylmalonic acidemia.

During an acute decompensation patients have ketoacidosis with an increased anion gap and ketonuria. Amino acid analysis may reveal elevations of valine, isoleucine, threonine, methionine, and glycine. Glutamine may be elevated due to hyperammonemia. Elevation of multiple organic acid metabolites can be observed, including methylmalonic acid and the same propionyl-CoA metabolites that accumulate in propionic acidemia (3-hydroxy-propionate, methylcitrate, tiglyglycine, tiglic acid, butanone, and propionylglycine). Propionylcarnitine (C3) elevation on the acylcarnitine profile is a marker for MMA in newborn screens that analyze acylcarnitine species using tandem mass spectroscopy. As in propionic acidemia, individuals with MMA can develop transient or chronic neutropenia and thrombocytopenia.

Treatment for MMA begins by determining if the patient has a defect in cobalamin synthesis. Cobalamin-responsive patients have a significant decrease in methylmalonic acid and propionic acid metabolites in organic acid analysis when given hydroxycobalamin 1 mg IM every day for 10 days. If responsive, then hydroxycobalamin 1 mg IM is given weekly. Cobalamin-responsive individuals have significantly fewer complications, less mortality, and require a diet that is less protein-restricted.[35] The diagnosis should be confirmed with molecular studies.

Prompt and aggressive metabolic management is required for acute metabolic decompensations in individuals with MMA. This treatment includes normal saline boluses for dehydration, liberal fluid resuscitation with 10% glucose solution at one and one-half to twice the maintenance rate, cessation of protein intake, and 2 g/kg/day intralipid administration for caloric supplementation as long as pancreatitis has been ruled out. Bicarbonate should be used carefully to correct severe acidosis. However, the provision of aggressive intravenous fluid hydration and adequate caloric intake to prevent catabolism will frequently help correct both acidosis and hyperammonemia. It is rarely necessary to treat hyperammonemia with sodium phenylacetate, sodium phenylbutyrate, and benzoate (see the following section, Urea Cycle Defects Associated with Acute Hyperammonemic Crises). Carnitine 200–300 mg/kg/day divided into two to four daily doses will help form propionylcarnitine esters that can be excreted in the urine. This helps to decrease the toxic levels of propionate and its metabolites that accumulate during an acute metabolic decompensation.

Dietary modification is the mainstay of chronic treatment for MMA.[36] Individuals with mut^0 and mut^- MMA must adhere to a rigid, protein restricted diet that limits the intake of valine, isoleucine, threonine, and methionine to the minimally required amount for normal growth and metabolism. This helps prevent the toxic accumulation of methylmalonic acid, propionic acid, and their metabolites. The diet also includes a special amino acid formula that contains all of the other essential amino acids. The required caloric needs

are provided through the generous use of carbohydrates and lipids. The diet recipe is adjusted based on the patient's growth and serial laboratory studies, including amino acid analysis, pH, and bicarbonate measurements. Carnitine at approximately 50 mg/kg/day is given chronically to help prevent the accumulation of propionate and its metabolites, and the dose can be adjusted based on the individual's quantitative carnitine levels. Intermittent use of metronidazole or neomycin helps to reduce the quantities of methylmalonate and propionate that are produced by intestinal flora, and this treatment can be especially efficacious during acute decompensations or when the patient develops constipation. Some patients have had liver transplantation[37] or combined liver kidney transplantation.[38] Transplantation decreases the risk of acute decompensations and there can be less restriction of protein in the diet, but it does not completely prevent the long-term neurologic sequelae.[39]

Mitochondrial cytopathies

The term *mitochondrial cytopathy* refers to a very large number of conditions that are due to impaired oxidative phosphorylation of the respiratory chain within the mitochondria. A detailed discussion of the genetics, clinical presentation and treatment of these conditions is beyond the scope of this chapter. Instead, a brief overview of this category of diseases and treatment principles will be provided.

The respiratory chain is comprised of five complexes, and each complex is a multimer of several enzymatic subunits. The five complexes contain a total of approximately 100 subunits. In addition, at least 60 other proteins are required to assemble the complexes. The majority of the subunits and all of the assembly proteins are encoded by nuclear DNA. Mutations in these genes can cause autosomal recessive, autosomal dominant or X-linked forms of mitochondrial cytopathies. However, most of these genes have not yet been identified and cloned.

Thirteen of the subunits of the respiratory chain complexes are encoded by mitochondrial DNA (mtDNA) genes. There are 16 569 base pairs within the mtDNA genome. This genome contains 37 genes, the 13 that encode subunits for the respiratory chain complexes, and 22 that encode the proteins required for translation of the mtDNA. The mtDNA genome has four unique features that adds additional complexity to the genetics of mitochondrial cytopathies: polyplasmy, heteroplasmy, threshold effect, and maternal inheritance. *Polyplasmy* is the presence of several copies of the mtDNA genome in a single cell, whereas there is a single copy of the nuclear DNA genome per cell. Furthermore, there may be mixed populations of normal and mutated mtDNA genomes in a single, or even within a single mitochondrion. This mixture of genomes is termed *heteroplasmy*. The degree of heteroplasmy can vary by tissue type within the same individual. Next, the *threshold effect* refers to the quantity or percentage of mutated mtDNA that must be present in a given tissue to cause mitochondrial dysfunction and an abnormal phenotype. This threshold is lower in tissues with higher energy requirements, such as the brain, heart, retina, and kidney. Thus, mutations of mtDNA are more likely to cause abnormalities in these tissues. Finally, a zygote only contains mitochondria from the oocyte. Thus, all the mtDNA within a zygote is from the oocyte. Thus, mtDNA diseases demonstrate a form of non-Mendelian inheritance called *maternal inheritance*.

The genetic complexity of mitochondrial cytopathies accounts for their protean clinical manifestations and broad variation in expressivity, even within the same family.[40] Almost any neurologic phenotype can occur in an individual with a mitochondrial cytopathy, including mental retardation, epilepsy, movement disorders, stroke, dementia, structural anomalies, leukodystrophy, headaches, myopathy, and axonal and demyelinating peripheral neuropathies.[41] Other potential clinical manifestations include, but are not limited to, cardiomyopathy, cardiac dysrhythmias, hearing loss, ophthalmoplegia, retinopathies, anemia, liver dysfunction, glomerulonephropathy, diabetes, and short stature. These clinical features may occur in isolation or in a variety of combinations, depending on the underlying genetic defect.

Although there are over 100 individual mitochondrial cytopathies, each is individually rare. Also, there can be considerable variation in the expressivity of a given mitochondrial disease. Therefore, it should not be surprising that there are very few controlled studies analyzing the efficacy of treatment for these diseases. For those small studies that have been published, the results unequivocally show that there is no clear benefit from any single medication regimen.[42] The most commonly used medication regimen is called the *mitochondrial cocktail*, a single mixture of several vitamins that act as cofactors of the complexes within the respiratory chain. Although this cocktail does not correct the underlying medical problems in most individuals with a mitochondrial cytopathy, it does provide significant amelioration of symptoms for a minority of individuals. Furthermore, it is safe. The most troubling side effects in diarrhea and intolerable taste, though a formulary pharmacy can usually mask the unpalatable taste. The cocktail includes carnitine (50–100 mg/kg/day), vitamin C (25 mg/ kg/day), thiamine (15 mg/kg/day), riboflavin (15 mg/kg/day), vitamin E (15 mg/kg/day), lipoic acid (15 mg/kg/day), pantothenate acid (15 mg/kg/day), and coenzyme Q_{10} (5–10 mg/ kg/day) (RI Kelley, personal communication, April, 2003).[43] Other supplements that can be added to the cocktail include folate (1–10 mg/ day) and selenium (25–50 mcg/day).[42] I recommend a three month treatment trial to determine if the vitamins are efficacious. If there has been no significant improvement within three months, then I recommend discontinuing the medications. Finally, symptomatic treatment of associated medical problems should also be provided, especially when the vitamin cocktail supplementation is ineffective or only partially effective.

Nonketotic hyperglycinemia

Nonketotic hyperglycinemia (NKH) is an autosomal recessive disorder due to impaired function of the glycine cleavage system. The glycine cleavage system is a mitochondrial enzyme complex that catalyzes the catabolism of glycine to ammonium and carbon dioxide. The complex is composed of four subunits: the P-protein, the T-protein, the H-protein, and the L-protein. The P-protein is encoded by the *GLDC* gene on chromosome 9, the T-protein is encoded by the *AMT* gene on chromosome 3, and the H-protein is encoded by the *GCSH* gene on chromosome 16. The gene for the *L*- protein has not been cloned. Except for one individual with a mutation in the *GCSH* gene, mutations occur in either the *GLDC* or *AMT* genes. Classically, neonates or young infants with NKH present with a rapidly deteriorating neurologic disorder following an asymptomatic period of variable length. Symptoms include seizures, lethargy that progresses to coma, hypotonia, apneic episodes, and hiccups. A variety of seizures can develop, including myoclonic, partial, tonic, clonic, and infantile spasms. If the diagnosis is unknown, severe apneic episodes frequently lead to intubation and mechanical ventilation. Most individuals die shortly after presentation, and those who survive have severe neurologic impairment. A later-onset form of NKH due to residual enzyme activity presents in later infancy. They also develop severe seizures, but do not have apneic episodes and severe hypotonia. Though they have mental retardation, they are not as severely impaired as those who survive the neonatal-onset form.

Decompensations are typically not associated with any abnormalities on routine laboratory studies. A burst-suppression pattern on the EEG may evolve into hypsarrhythmia. Magnetic resonance imaging of the brain may show a variety of malformations, such as agenesis or hypoplasia of the corpus callosum, parietooccipital white matter changes, and increased signal intensity of the basal ganglia. Amino acid analysis reveals elevations of glycine in both the plasma and cerebrospinal fluid. The normal cerebrospinal fluid/plasma glycine ratio is 0.02 or less. If the cerebrospinal fluid is uncontaminated with blood, then a cerebrospinal fluid/ plasma glycine level of 0.2 or greater is highly suggestive of NKH.[44] Late-onset NKH typically shows a ratio of 0.09 or greater.

Treatment of the classic form of NKH includes benzoate and dextromethorphan. Benzoate binds to glycine to form hippurate, which is subsequently voided in urine. Benzoate supplementation (500–750 mg/kg/day) is associated with decreased seizure frequency, but it does not improve neurologic outcome.[45,46] Dextromethorphan is an NMDA antagonist, and it is believed to block the glycine-mediated excitotoxicity at NMDA receptors. Dextromethorphan (5–20 mg/kg/day) has been associated with decreased seizure frequency and improved developmental outcome.[47] Other anticonvulsant therapy may be necessary.

Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive disorder due to phenylalanine hydroxylase enzyme deficiency. This enzyme catalyzes the conversion of phenylalanine to tyrosine. Tetrahydrobiopterin is a cofactor of the enzyme. The monomeric enzyme is encoded by the *PAH* gene on chromosome 12. Untreated PKU primarily causes severe mental retardation, and this may be the only manifestation of the disease. Other less common neurologic features include spastic cerebral palsy, epilepsy, movement disorders, hyperactivity, microcephaly, and delayed myelination. A pruritic dermatitis may also develop. However, untreated PKU is quite rare because this disorder was one of the first inborn metabolic diseases to be diagnosed in presymptomatic neonates through the newborn screening program. Phenylalanine or one of its by-products is a teratogen, and poorly controlled PKU in a mother causes severe microcephaly, mental retardation, and an increased risk of congenital heart disease in her offspring.

As mentioned previously, PKU is typically diagnosed in an otherwise healthy, nondysmorphic newborn infant whose newborn screen reveals a markedly elevated phenylalanine level. Levels of 1200 µmol or greater are diagnostic. The diagnosis can be confirmed with *PAH* mutation analysis. Also, a defect in the synthesis of tetra hydrobiopterin, the cofactor for phenylalanine hydroxylase, should be ruled out in all individuals with elevated phenylalanine levels (greater than 600 µmol).

It is important to promptly institute a phenylalanine-free diet in newborns with classic PKU. Depending on the level of the phenylalanine at the time of diagnosis, a phenylalanine-free formula is provided for the first few days, and a follow-up phenylalanine level is obtained in one to three days. Once the phenylalanine level reaches the treatment range (120 µmol-360 µmol), a restricted phenylalanine diet is reintroduced. Long-term adherence to a phenylalanine-restricted diet prevents long-term sequelae.

In the past the diet was discontinued at approximately age 5–8. Once phenylalanine restriction is discontinued and protein is introduced into the diet, it can be very difficult to restart the diet. This can become particularly problematic for young women with PKU who discontinued the diet in childhood and are now pregnant. Decreasing the phenylalanine levels to the treatment range within the first 10–12 weeks of gestation may result in a good fetal outcome,[48] but initiation of the rigid and unpalatable phenylalanine-restricted diet will probably require admission to the hospital. Life-long adherence to the diet is now recommended for all individuals with PKU.[49]

Tetrahydrobiopterin therapy for some individuals with PKU has shown considerable promise. Individuals with PKU may have null mut ations or missense mutations. While null mutations result in no enzyme production, many missense mutations produce some residual enzyme activity. In individuals with PKU who have at least one missense mutation, there will typically be residual PAH activity. Some of these individuals have been shown to respond to pharmacological doses of tetrahydrobiopterin, the cofactor of PAH.[50] In those individuals who are responsive to tetrahydrobiopterin, their phenylalanine-restricted diet can be liberalized.

Propionic acidemia

Propionic acidemia (PA) is an autosomal recessive disorder due to propionyl-CoA carboxylase enzyme deficiency. This enzyme catabolizes valine, isoleucine, threonine, methionine, odd-chain fatty acids, and cholesterol by catalyzing the conversion of propionyl-CoA to methylmalonyl-CoA. The enzyme is composed of two subunits, α and β, to form a multimeric complex, $\alpha_4\beta_4$. The α subunit is encoded by the *PCCA* gene on chromosome 13, and the β subunit is encoded by the PCCB gene on chromosome 3. Propionic acidemia causes recurrent attacks of ketoacidosis that causes severe vomiting, lethargy that can progress to coma, and brain injury or death, even if treated aggressively. Ketoacidotic episodes can be triggered by any metabolic stress, including a protein load in the diet, infections, or prolonged fasting. In addition to the lethargy and coma that can present during acute episodes, other neurologic features that can occur in patients with PA include infantile hypotonia that may evolve into hypertonia and spastic tetraparesis, global developmental delay and mental retardation, epilepsy, dystonia, choreoathetosis, and brain atrophy. There are reports of strokes in individuals with PA, and I have had a patient experience bilateral basal ganglia strokes at the onset of an influenza infection. Osteoporosis, recurrent pancreatitis, and cardiomyopathy can occur.

Laboratory characteristics of PA during an acute decompensation include ketoacidosis with an increased anion gap (due to accumulation of 3-hydroxybutyrate, acetoacetate, lactate, and propionate) and ketonuria. Before the underlying defect was identified, PA was called ketotic hyperglycinemia because glycine is elevated in the blood. In acute decompensations there may be elevations of the amino acids that are metabolized by propionyl-CoA carboxylase, including valine, isoleucine, threonine, and methionine. Some patients have hyperammonemia during acute episodes, and this may be associated with hyperglutaminemia in amino acid analysis. Characteristic organic acid metabolites are 3-hydroxypropionate and methylcitrate, and tiglyglycine, tiglic acid, butanone, and propionylglycine may also be elevated. Propionylacyl carnitine (C3) is elevated on acylcarnitine profile analysis, and this may be detected on newborn screens that include measurement of acylcar nitine species. Due to chronic bone marrow suppression, individuals with PA may have neutropenia, thrombocytopenia or pancytopenia.

As with MMA, metabolic decompensations in a patient with PA require aggressive emergency treatment. This treatment includes fluid boluses with normal saline if the patient is dehydrated and ongoing fluid resuscitation with 10% glucose intravenous fluids at 11/2 to twice the maintenance rate. The large quantities of glucose combined with protein restriction prevent catabolism of endogenous or exogenous protein. If pancreatitis has been ruled out, then intralipid 2 g/kg/day can help prevent protein catabolism by providing additional caloric supplementation. Acidosis should be carefully corrected with bicarbonate administration. Hyperammonemia may rarely require treatment with sodium benzoate and phenylacetate because the elevated ammonium typically resolves with carbohydrate and fluid administration. Propionyl CoA impairs the function of the Krebs cycle, but carnitine binds to propionyl CoA to form a soluble ester that can be excreted in the urine. Therefore, to decrease the build up of propionate and propionyl CoA, patients should be given carnitine 200–300 mg/kg/day divided into three or four daily doses during acute episodes.

The principle method of chronic treatment for PA is dietary modification. Like those affected with mut^0 and mut-MMA, individuals with PA must adhere to a rigid, protein restricted diet that limits the intake of valine, isoleucine, threonine, and methionine to the minimally required amount for growth and metabolism. This helps prevent the toxic accumulation of propionic acid and its metabolites. The diet also includes a special amino acid formula that contains all of the other essential amino acids. The required caloric needs are provided through the generous use of carbohydrates and lipids. The diet recipe is adjusted based on the patient's growth and serial laboratory studies, including amino acid analysis, pH, and bicarbonate measurements. Carnitine at approximately 50 mg/kg/day is given chronically to help prevent the accumulation of propionate and its metabolites, and the dose can be adjusted based on the individual's quantitative carnitine levels. Intermittent use of metronidazole or neomycin helps to reduce the quantities of methylmalonate and propionate that are produced by intestinal flora, and this treatment can be especially efficacious during acute decompensations or when the patient develops constipation. Biotin is a cofactor of propionyl CoA carboxylase and is frequently prescribed, but its efficacy has never been proven. Some patients have had liver transplants because this decreases the accumulation of propionate and its metabolites and may help prevent ketoaci dotic decompensations.[51] Even with adequate medical management, many patients have mental retardation and other chronic problems.

Pyridoxine-responsive seizures

The pyridoxine-responsive seizure disorder is an autosomal recessive condition due to deficiency of the enzyme antiquitin. This enzyme catalyzes the conversion of 2-aminoadipic-6 semialdehyde to 2-aminoadipic in the catabolism of lysine and hydroxylysine. The enzyme is composed of a monomer that is encoded by the *ALDH7A1* gene on chromosome 5. Affected individuals typically present with the onset of seizures in utero or shortly after birth. Several different seizure types may occur, including partial and generalized, tonic-clonic, infantile spasms, and atonic seizures. Progression to recurrent status epilepticus is common. Other neurologic features include irritability, nystagmus, and other eye movement abnormalities.[52] Rarely, this disorder may present in late infancy. Without treatment the seizures can become resistant to all medications, and affected individuals may die from the disorder.

At this time diagnosis of pyridoxine responsive seizures is based on the effect that pyridoxine administration has on the electroencephalogram pattern. In this disorder, the EEG classically shows a burst suppression. While an EEG is being obtained, pyridoxine 50–100 mg is administered intravenously.[53] Following this infusion, the electrographic seizures will abate within a few minutes in individuals who are responsive to pyridoxine. Possible side effects of this treatment include apnea and hypotension. If the pyridoxine infusion is efficacious, then oral pyridoxine 5–10 mg/kg/day should be provided. Though affected individuals may have breakthrough seizures and learning disabilities, they do not usually experience long-term cognitive impairment.

Though pyridoxine if extremely effective in this disorder, it is not a cofactor of antiquitin. In addition to discovering that antiquitin deficiency was the etiology for pyridoxine-responsive seizures, Mills and colleagues have offered an explanation for the efficacy of this vitamin in a seemingly unrelated disorder of lysine metabolism.[54] Antiquitin deficiency leads to an accumulation of 2-aminoadipic-6-semialdehyde, which is converted to piperidine-6-carboxylic acid. This compound subsequently binds to pyridoxal phosphate, the active form of vitamin B6. Thus, affected individuals need pyridoxine supplementation to replete the secondary loss of pyridoxal phosphate.

Urea cycle defects associated with acute hyperammonemic crises

The function of the urea cycle is to excrete excess nitrogen by converting ammonium into a water-soluble compound, urea. There are five enzymatic steps in this cycle (see Table 12–1). In addition, the first enzyme, carbamyl phosphate synthetase, requires an activator, N-acetylglutamate. The synthesis of N-acetylglutamate is catalyzed by the enzyme N-acetylglutamate synthetase. Deficiencies of the first four enzymes in the pathway and a deficiency of N-acetylglutamate synthetase lead to acute encephalopathy crisis due to rapidly rising ammonium levels. Neonates with a urea cycle defect may present in the first few days of life. They develop feeding difficulties, vomiting, and lethargy. If untreated the babies can develop seizures, apnea, and coma. Death may occur from cerebral or pulmonary hemorrhage, and those who survive have severe neurologic impairment. Some individuals do not present until later in their first year of life because they have residual enzyme activity. Precipitants of a hyperammonemic crisis include a high-protein meal or catabolic stress such as an infection or fasting.

Table 12–1 Urea Cycle Defects

Enzyme	Reaction	Inheritance	Distinctive Features
N-acetylglutamate synthetase	Acetyl-CoA + glutamate → N-acetylglutamate	AR	Hyperammonemic crisis Very rare Normal arginine, citrulline, orotic acid
Carbamyl phosphate synthetase (Activator: N-acetylglutamate)	NH+ + HCO3 + ATP → carbamyl phosphate	AR	Hyperammonemic crisis Low arginine and citrulline Normal orotic acid level
Ornithine transcarbamylase	Carbamyl phosphate + ornithine → citrulline	X-linked	Hyperammonemic crisis Low arginine and citrulline Elevated orotic acid
Argininosuccinate synthetase (Citrullinemia)	Citrulline + aspartate → argininosuccinate	AR	Hyperammonemic crisis Very high citrulline Low arginine Moderate orotic acid elevation
Argininosuccinate lyase	Argininosuccinate → arginine + fumarate	AR	Hyperammonemic crisis Elevated citrulline Moderate orotic acid elevation Hepatomegaly may occur Trichorrhexis nodosa Mildly elevated transaminases
Arginase	Arginine → urea + ornithine	AR	Spastic diplegia May have episodes of hyperammonemia Elevated arginine lysine, ornithine, and cystine

Arginase is the last enzyme in the urea cycle. It produces ornithine and urea from arginine. Arginase deficiency causes spastic cerebral palsy, epilepsy, ataxia, and dystonia. It very rarely causes acute encephalopathy.

During an acute metabolic decompensation, the ammonium level can be very high. Elevated ammonium can stimulate the respiratory drive; therefore, early in the course of a hyperammonemic crisis, the affected individual may have a secondary respiratory alkalosis. Plasma amino acid analysis reveals elevated glutamine and alanine. The levels of citrulline and arginine can help clarify which enzyme is defective. The presence or absence of orotic acid in urine is also a helpful distinguishing feature of the urea cycle enzymes. Liver transaminase levels may be elevated.

Acute hyperammonemia is a medical emergency. Protein intake must be discontinued, and catabolism must be abated. As with the management of acute decompensation from an organic aciduria, dehydration should be treated with normal saline fluid boluses. Furthermore, ongoing fluid resuscitation with 10% glucose intravenous fluids at 11/2 to twice the maintenance rate is also required. The large quantities of gl ucose combined with protein restriction prevent catabolism of endogenous or exogenous protein, thus decreasing the production of endogenous ammonium. Intralipid 2 g/kg/day can help prevent protein catabolism by providing additional caloric supplementation.

If hyperammonemia is very high (>200 μmol/L), then pharmacologic agents that scavenge nitrogen must be used. Glycine and glutamine are in equilibrium with ammonium. Benzoate conjugates with glycine to form hippurate, and phenylbutyrate and phenylacetate conjugate with glutamine to form phenylglutamine. Both hippurate and phenylglutamine are water-soluble, and these medications provide an alternative to urea for excreting nitrogen. In addition, arginine becomes an essential amino acid when the urea cycle is dysfunction.

In the United States, these medications are provided as a single intravenous formulation called Ammonul in 10% dextrose. A loading dose of Ammonul is given over 90 minutes, and the same total quantity of medication is then given over the following 24 hours as a maintenance dose.[55] The recommended dose for phenylacetate, phenylbutyrate and benzoate is 2.5 mL/kg (250 mg/kg) for babies and young children and 5.5 g/m^2 (55 mL/m^2) for older children and adults. The dose of arginine HCl is depends on the specific urea cycle defect that is being treated. For individuals with a possible urea cycle defect, argininosuccinate synthetase deficiency, or argininosuccinate lyase deficiency, the dose of arginine HCl is 600 mg/ kg (6 mL/kg). For babies and young children with carbamyl phosphate synthetase deficiency or ornithine transcarbamylase deficiency, the dose is 200 mg/kg (2 mL/kg). Potential side effects from these medications include nausea, vomiting, and low blood pressure. Ammonium levels are monitored regularly, including at the beginning of loading dose, once the loading dose is completed, and every 4–8 hours thereafter, depending on the ammonium level and the rate of rise or fall of the level. If the scavenger medications are ineffective or unavailable, then hemodialysis should be performed to quickly and efficiently decrease the level.

Chronic treatment for a urea cycle defect includes a low protein diet that is adjusted to provide adequate protein intake for normal growth and development. In order to provide adequate calories, a protein-free formula is usually used in combination with another formula or table food. In addition, oral formulations of the nitrogen scavenger medications are prescribed, including sodium phenylbutyrate and citrulline.

Prompt acute treatment is essential for avoiding brain injury from the cerebral edema that develops secondary to hyperammonemia. This edema can cause irreversible neurologic impairment or death, and the risk of edema and injury exists with each hyperammonemic episodes. However, the first episode of hyperammonemia presents the highest risk for neurologic injury because the underlying diagnosis is usually unknown, the symptoms of hyperammonemia are rare, and even a short delay in the initiation of treatment can lead to serious complications. Since the ammonium level can rise very rapidly from even a minor illness, many families of children with severe urea cycle defects consider liver transplantation because the transplantation abolishes the need for a low protein diet and the risk of brain injury or death from hyperammonemia.

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Psychiatric Disorders

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Since the previous edition of this chapter, the field of psychiatry has undergone a paradigm shift more dramatic than perhaps in any other area of medicine. Three major technical and conceptual advances account for this transformation. First, the tremendous advances in neuroscience research have provided a progressively more sophisticated understanding of brain development, neural systems functions and cognition.[1] Perhaps the most compelling insight relevant to psychiatric disorders is that the brain is a remarkably plastic organ that exhibits both functional as well as structural changes as a consequence of environmental interactions and even mentation itself. Second, advances in brain imaging have permitted high-resolution measurement of brain structure, function, and chemistry.[2–4] Quantitative morphometry has unequivocally demonstrated the distributed cortical pathology of schizophrenia as well as atrophy of the hippocampus in major depressive disorder and posttraumatic stress disorder, for example. Functional brain imaging has documented region and pathway specific abnormalities in neuronal activity in response to specific cognitive/emotional challenges in disorders as diverse as major depression, obsessive-compulsive disorder and schizophrenia. Finally, the human genome project has deeply affected psychiatry with compelling evidence that serious psychiatric disorders have a substantial genetic component.[5] We now know that psychiatric disorders are likely due to complex genetics with multiple risk genes of modest effect interacting with environment to produce the phenotype. Putative risk genes for psychiatric disorders are being identified at an accelerating rate. The genetic deconstruction of psychiatric disorders will offer opportunities for pharmacologic interventions that are targeted at the molecular mechanisms responsible for components of psychiatric disorders so that in the future personalized medicine will likely affect psychiatry as much as other areas of medicine.

Clinical psychopharmacology

Before considering specific classes of psychotropic drugs, it would be useful to review briefly the strategies that have permitted the identification of drugs with unique and specific psychotherapeutic effects. The dawn of rational psychopharmacology came with the discovery in the early 1950s that chlorpromazine reduced psychotic symptoms in patients suffering from schizophrenia. Needless to say, this assertion was met with considerable skepticism because of the belief prevalent at the time that schizophrenia was the psychological consequence of destructive early life experiences. Thus, in this context, it was necessary to prove that the drug was effective in a disorder, for which no brain pathology had been identified and the etiology of which remained obscure. This challenge was met with the first major double-blind placebo controlled trial conducted in psychiatry, the National Institute of Mental Health-Veterans Administration (NIMH-VA) study of chlorpromazine.[6] Double-blind refers to the fact that neither the patient nor the treating (or evaluating) physician knows whether the patient is receiving an active drug or placebo. This strategy controls for the possibility that patients might experience reduction in symptoms as a consequence of the nonspecific effects of the therapeutic intervention. Blindness of the evaluating physician prevents conscious or unconscious biases with regard to the therapeutic impact of the drug. In these early studies, symptoms in patients were titrated with the drugs, which allowed for the determination of the dose that results in the optimal therapeutic response.

These pioneering studies demonstrated that chlorpromazine significantly reduced the psychotic symptoms of patients suffering from schizophrenia, that it was clearly superior to placebo and that this was not due to sedation since the sedative phenobarbital, the active comparator, was no more effective than placebo. With the subsequent development of analogues of chlorpromazine or novel structures that had behavioral characteristics similar to chlorpromazine (such as preventing apomorphine induced emesis in dogs), each was subjected to the same method of clinical trial, often in comparison with chlorpromazine as the effective standard.[7] Finally, while extrapyramidal side effects and sedation were a common occurrence with these agents, these side effects did not correlate with therapeutic action.

The double-blind placebo-controlled clinical trial is now the golden standard to which virtually all new drugs are subjected. The structural activity relationships generated for each class of drugs that devolve from these clinical trials have facilitated the search for molecular sites of action of psychotropic drugs including antipsychotics, antidepressants and benzodiazepines. This information permitted the development of correlations between the clinical efficacy and potency of a class of psychotropic

medications and their interactions with specific brain parameters. For example, a compelling correlation between the potency of the antipsychotics and their affinity for dopamine D2 receptors was demonstrated based on the results of clinical trials.[8]

It is important, however, to recognize the limitations of the double-blind placebocontrolled studies for understanding how psychotropic medications work in real world clinical settings. Clinical trials of efficacy are carried out in highly selected populations subject to many exclusionary criteria including age, comorbid medical conditions, substance abuse and other comorbid psychiatric disorders. In recent years, carefully designed effectiveness trials involving a substantial number of patients with few exclusionary criteria treated in regular clinics have provided a more realistic and tempered appraisal of the effectiveness of antidepressants and antipsychotics and have raised questions about the perceived superiority of newer “on-patent” drugs versus older off-patent drugs.[9,10] Nevertheless, the clinician now has a broad array of antipsychotics, antidepressants and mood stabilizers with somewhat differing clinical effects and side effects from which to choose. In spite of this broad array, it is sobering to note that the basic mechanisms of therapeutic actions of the antidepressants and the antipsychotics remain the same as understood over a quarter of a century ago. Truly novel drugs are wanting, especially for those patients who respond poorly to existing psychotropic medications.

Antipsychotics

Schizophrenia

Psychosis is a syndrome, in which the individual holds firm beliefs (delusions) and experiences abnormal perceptions (hallucinations) that are not grounded in reality but with no impairments in consciousness. While psychosis has been historically considered a core component of schizophrenia, it can occur in a variety of neuropsychiatric conditions including major depressive disorder, mania, dementia and drug induced states. But, for the sake of discussion, the features of schizophrenia, which is the primary target of antipsychotic treatment, will be reviewed.

Schizophrenia is a particularly malignant, chronic psychiatric disorder that typically has its age of symptomatic onset in late adolescence and young adulthood. It is more common in males whereas females tend to have a later age of onset and a less malignant course. Although schizophrenia affects only 1% of the population, it is the seventh most costly medical disorder in terms of direct treatment costs and loss of wages because most patients remain disabled throughout their adulthood.

Schizophrenia exhibits familial aggregation with a high degree of heritability (0.8). Thus, the morbid risk in first-degree relatives of a proband is 10–14 times greater than that of the general population and the concordance for identical twins, if one is affected, is approximately 50%.[11] This inheritance pattern is consistent with schizophrenia being a disorder of complex genetics in which multiple genes of modest effects interact with environmental factors to produce the phenotype. Salient environmental factors appear to be perinatal insults including viral infection, famine and hypoxia. Ongoing linkage and association studies have identified approximately 15 putative risk genes, which fall into three categories: genes regulating brain development, genes involved in synaptic neurotransmission (glutamate, acetylcholine, dopamine) and genes associated with glia.[12]

Table 13–1 lists a summary of the *Diagnostic and Statistical Manual (DSM—IV)* diagnostic criteria for schizophrenia. A useful way of categorizing the symptoms of schizophrenia is to distinguish the positive symptoms from the negative symptoms and cognitive impairments. Positive symptoms include hallucinations, delusions, agitation and thought disorder. These symptoms are often the most dramatic and bring the patient to the attention of the physician. The negative symptoms, however, are the more disabling because they persist over time, often becoming more severe with age whereas the positive symptoms wax and wane and often become less prominent in the aged schizophrenic. Negative symptoms include social withdrawal, social incompetence and loss of drive. Recent research has documented a range of cognitive impairments that affect memory, problem solving and executive functions that validate Kraeplin’s concept of *dementia praecox*. Negative symptoms and cognitive impairments correlate with the degree of cortical atrophy and ventricular enlargement, which can progress for 5 to 10 years after the symptomatic onset of the disorder.[13]

Table 13–1 Schizophrenia

1. Two or more characteristic symptoms: delusions, hallucinations, disorganized speech, disorganized behavior, or negative symptoms (blunted affect, sparse speech)
2. Social/occupation dysfunction
3. Symptoms persist for at least six months
4. Not due to a drug or a medical condition

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.[78]

Clinical evidence indicates that positive symptoms are the most responsive to antipsychotics whereas the negative symptoms and cognitive impairments are minimally responsive or unresponsive, with the possible exception of clozapine (see further on in this chapter). This distinction is important for several reasons. First, it reifies the evidence that antipsychotics are not a cure for schizophrenia. To the contrary, most patients suffering from schizophrenia remain incapacitated in spite of optimal treatment with antipsychotics. Second, this suggests that the site of therapeutic action of antipsychotics represents an ancillary but not necessarily the causative defect in schizophrenia. And finally, it directs the physician’s attention to the endpoint of effective symptomatic management of patients with schizophrenia using antipsychotics.

Site of Action of Antipsychotics

The propensity of the early antipsychotics such as chlorpromazine to produce Parkinsonian side effects pointed to the dopaminergic system as a potential site of action of these drugs. This connection was strengthened by the demonstration that reserpine, a drug that depletes the brain of biogenic amines by irreversibly inhibiting the vesicular transporter, also exhibited antipsychotic efficacy. Carlsson and Lindquist[14] first proposed that antipsychotics act by blocking the brain’s receptors for dopamine. Carlsson’s hypothesis, for which he received the Nobel Prize in 2000, was confirmed with the development of ligand binding techniques to identify receptors. Using [3H] haloperidol as a ligand, Creese and associates[8] were able to demonstrate a recognition site to which it bound with high affinity and was displaced by dopamine and other dopamine receptor agonists. There was a remarkably high correlation between the clinical potency of all antipsychotics, regardless of chemical structure, and their ability to compete at the receptor recognition site labeled by [3H] haloperidol. This receptor was designated dopamine D-2 receptor as it was discovered after the dopamine activated adenylyl cyclase, which was designated the dopamine D-1 receptor.

Subsequently, the dopamine receptors were cloned and shown to consist of two families: D-1and D-5, which are positively coupled adenylyl cyclase, and D-2, D-3, and D-4, which are negatively coupled to adenylyl cyclase.[15] Notably, D-3 and to a lesser extent D-4 have a more limited regional expression primarily in cortical limbic regions of the brain, which has raised questions whether some of the therapeutic actions of antipsychotics may be mediated by these other two receptors. However, D-3 and D-4 specific antagonists have not proved to be clinically effective thus far. All antipsychotic medications appear to exert their therapeutic effects through blockade dopamine D-2 receptors, even aripiprazole, a partial D-2 receptor agonist, which is associated with approximately 80% D-2 antagonism at therapeutic doses. Indeed, in vivo positron emission tomagraphy (PET) ligand binding studies for the dopamine receptor in human brain indicate that with the exception of clozapine antipsychotic efficacy is associated with 70%–80% blockade of dopamine D-2 receptors.[16]

Clozapine and the Second-Generation Antipsychotics

The antipsychotic, clozapine, had an unusual clinical profile with a complete absence of extrapyramidal side effects, but it was discontinued because of the occurrence of agranulocytosis. It was resurrected by academic investigators and shown to have a number of intriguing features.[17] First, it did not cause extrapyramidal side effects and even

reduced the symptoms of tardive dyskinesia. Second, it proved effective in a subpopulation of patients who responded poorly to other antipsychotic medications. Third, in many patients it had remarkable effects on negative symptoms, the therapeutic effects ofwhich typically evolved gradually over a period of several months. Finally, it appeared to have unique effects on the anhedonic component of schizophrenia, significantly reducing suicide, smoking and substance abuse. Recent meta-analyses as well as head-to-head comparison in effectiveness studies indicate that clozapine is significantly better than all other antipsychotic medications.[18,19] The deterrent to broad use of clozapine is a requirement for regular blood tests to monitor for agranulocytosis (weekly for first six months, biweekly the next six months, and monthly thereafter) and a high risk for substantial weight gain with attendant hyperlipidemia, type II diabetes and metabolic syndrome.

Pharmaceutical companies have attempted to tease out the critical receptor interactions that may contribute to this profile of chlozapine. Blockade of 5HT2A receptors appears to account for the low propensity for extrapyramidal side effects. This feature was designed into several of the second-generation antipsychotics including risperidone, olanzapine, quetiapine, and ziprasidone (Table 13–2). Olanzapine most closely mimics the receptor profile of clozapine affecting in addition the α1 adrenergic, H1 histaminergic and M1 muscarinic receptors. Olanzapine like clozapine has a high risk for substantial weight gain, hyperlipidemia and metabolic syndrome although the FDA has raised concerns about this side effect profile for all second-generation antipsychotics as a class.[20]



Table 13–2 Atypical Antipsychotics

	Therapeutic Range (mg/day)
Clozapine	150–450
Risperidone	4–6
Olanzapine	20–30
Quetiapine	300–600
Sertindole	12–20
Ziprasidone	20–80
Aripiprazole	15–30

Clinical Use of Antipsychotics

The primary indication for antipsychotic treatment is the management of the positive symptoms of schizophrenia.[21] In addition, antipsychotics can be useful in symptomatic management of psychotic symptoms that occur in mania and in major depressive disorder although antipsychotics are usually prescribed in combination with more specific pharmacologic interventions for these disorders such as lithium or valproic acid for mania and antidepressants for psychotic depression.[22] In the case of schizophrenia, antipsychotics are used in two contexts: the acute management of a psychotic episode and then as a prophylaxis to prevent recurrence of psychosis.

If the patient is presenting with their first psychotic episode or has been treated for less than a year, the common practice is to commence treatment with a second generation antipsychotic such as risperidone, olanzapine, or quetiapine.[23] Gradual dose escalation should be evaluated over the following three weeks, depending upon symptom response. Improvement in overall behavior such as decreased agitation and seclusiveness and increased attention to activities of daily living heralds the resolution of the psychotic episode. Reduction of the intrapsychic symptoms such as delusions and auditory hallucinations often lags behind behavioral improvement although the patient is apparently less preoccupied with these psychotic experiences. As the acute psychotic episode resolves, many patients become more sensitive to the sedating affects of antipsychotics. At this point, dosage reduction may be considered, which should proceed slowly and incrementally with careful monitoring for recurrence or exacerbation of psychotic symptoms. As the optimal dose is achieved with resolution of the psychosis, the dose should be maintained for a period of six months to a year, at which time, diagnosis and even the requirement for continued treatment with antipsychotics need to be evaluated.

Maintenance or prophylactic treatment with antipsychotics should be restricted to patients for whom there is clear evidence that the disorder is chronic because of the risk of serious side effects such as tardive dyskinesia, weight gain and/or hyperprolactinemia. Continuous treatment with antipsychotic medication has long been established as the optimal approach for patients suffering with schizophrenia.[21] Controlled studies have demonstrated that recurrence of psychosis occurs at nearly three times the rate when placebo is substituted for active drug, and lack of adherence is a major cause for relapse. The goals of maintenance treatment are to prevent relapse, minimize adverse affects and insure adherence with treatment. Adherence to treatment is greatly improved when pharmacotherapy is incorporated into appropriate psychosocial interventions. Clinical studies indicate that maintenance therapy typically involves a use of doses 2- to 3-fold less than those associated with treatment of acute psychotic episode, which reduces the risk for adverse side effects. Recent studies suggest that there may be little advantage of second generation antipsychotics over the off-patent first generation drugs with regard to patient tolerability.[9] Aripiprazole, however, is an attractive maintenance treatment because of the absence of extrapyramidal side effects, weight gain or elevated prolactin.[24]

A substantial number of patients in the chronic phase of schizophrenia have poor insight into their disorder and thus present with recurrent psychosis due to poor adherence with pharmacotherapy. To circumvent this problem, long-acting injectable antipsychotics such as haloperidol, fluphenazine or resperidol, which are linked to a lipid such as decanoate, can provide stable blood levels for up to four weeks after a single injection. Lack of adherence is obvious when the patient does not keep his clinical appointment, and appropriate steps can then be taken.[25]

Side Effects of Antipsychotics

The dopamine D-2 receptor that accounts for the antipsychotic effects of these drugs also mediates the action of dopamine in the basal ganglia and pituitary.[26] Thus, neurologic and neuroendocrine side effects are a common and predictable complication of antipsychotic treatment, especially with the first generation of drugs. Clinicians need to pay attention to these side effects because they are a major source of patients' reluctance to adhere to treatment. The motor rigidity, masked facies and gynacomastia can be stigmatizing and thereby interfere with the reintegration of patients into their social setting. Antipsychotics can, on occasion, have medically serious if not fatal consequences such as malignant hyperthermia (see further on in this chapter).

The three most common acute neurologic side effects are Parkinsonian symptoms, dystonic reactions, and akathisia. Parkinsonian symptoms include tremor, bradykinesia and rigidity as well as the associated signs of masked facies, stooped posture, and drooling. The risk for Parkinsonian side effects increases with age. Dystonic reactions typically present as episodic or persistent cramping of muscles, especially near the midline and include occulogyric crisis, opisthotonos, torticollis and pharyngeal/lingual spasm. Dystonic symptoms can wax and wane and may transiently disappear when the patient is distracted. Their bizarre appearance and variability often lead to the misimpression that they are hysterical in nature because of the underlying psychiatric disorder. Dystonic reactions occur more frequently in younger patients.

Akathisia represents an inner sense of restlessness that may be manifest in mild form as fidgetiness and in severe forms as ceaseless agitation.[27] Akathisia may be

misinterpreted as a recrudescence of the psychosis, prompting larger doses of antipsychotics, there by further exacerbating the symptoms. When asked, many patients can distinguish the peripheral manifestations of akathisia from the psychic symptoms of their underlying disorder. The safest avenue is to assume that any striking motoric symptoms in a patient receiving antipsychotics represents a drug side-effect that is not simply a manifestation of underlying psychopathology.

The neurocircuitry underlying these acute extrapyramidal side-effects is well understood.[26] Blockade of dopamine D-2 receptors on striatal cholinergic interneurons results in their disinhibition and excessive stimulation of postsynaptic muscarinic receptors. Drugs that block muscarinic cholinergic receptors have been used effectively since the days of Charcot to treat the extrapyramidal symptoms caused by impaired dopaminergic function. These classic antiparkinsonian anticholinergic medications are available in a variety of structures although benztropine is the one most commonly used because of its specificity and low affinity for histamine H1 receptors, the blockade of which causes sedation. Nevertheless, the ability of anticholinergic drugs to reverse the neurologic side effects of antipsychotics is not uniform. Dystonic reactions and rigidity appear to be most responsive whereas bradykinesia and especially akathisia are much less responsive. Akathisia can occur both with the first generation as well as the second generation antipsychotics that have a lower risk for Parkinsonian side effects.[28] Dose reduction or the adjunctive use of a beta-adrenergic antagonist such as propranolol may attenuate akathisia.

A potentially irreversible neurologic complication of long-term antipsychotic treatment is tardive dyskinesia.[29] This disorder is characterized by pulsive movements of the tongue, facial grimacing and vacuous chewing in its mild form but can proceed to choreoathetotic movements of the extremities and a lordotic posture. Kane suggests a 3%–5% annual incidence of tardive dyskinesia in patients receiving first generation antipsychotics and 1% rate with the second generation antipsychotics except for clozapine, which appears to bear no risk.

The etiology of tardive dyskinesia remains obscure. Interestingly, there is compelling evidence of similar movement disorders in chronic schizophrenic patients prior to the introduction of antipsychotics or in countries where antipsychotics are not available. Irreversible supersensitivity of D-2 receptors as a result of chronic receptor blockade is a plausible hypothesis although it is not supported by postmortem studies. Studies in experimental animals indicate that prolonged administration of high potency antipsychotics causes degeneration of striatal GAB-Aergic interneurons analogous to Huntington's disease.[30] In addition, emerging evidence from pharmacogenetic studies suggests that allelic variants of genes associated with dopaminergic neurotransmission and hepatic metabolism of antipsychotics may affect vulnerability.[31]

An uncommon but by no means rare complication of antipsychotic treatment of particular relevance to neurologists is the neuroleptic malignant syndrome (NMS). Although fewer than 50 case reports describing the syndrome appeared in the word literature during the first 20 years of antipsychotic usage, more recent research suggests that symptomatic manifestations of NMS may affect approximately 1% of patients treated with antipsychotics.[32] The second-generation antipsychotics including clozapine are not immune from this potentially lethal condition.[33] Neurologists should be especially sensitive to this complication because they are likely to be consulted in the evaluation of patients presenting with the cardinal symptoms of NMS: profound rigidity, fever of unknown origin, delirium, and rhabdomyolysis. Furthermore, with the increasing use of antipsychotics to treat psychotic complications of neurologic disorders and the evidence that this syndrome may be precipitated by abrupt withdrawal of antiparkinsonian agents in patients with Parkinson's syndrome, it is now evident that NMS is a complication not unique to psychiatric patients.[34]

While there is debate about the pathophysiology of NMS, the most parsimonious explanation is that it represents a severe extrapyramidal syndrome resulting from insufficient stimulation of dopamine receptors. While it shares many features with malignant hyperthermia, most studies indicate that patients suffering from NMS do not exhibit the same muscular metabolic defect that is responsible for malignant hyperthermia. Certain risk factors such as extreme heat, dehydration and acute increase in neuroleptic dosage may predispose for the development of NMS.[35] Such interactions best explain the observation that many patients, who have developed NMS, do not exhibit a recurrence of symptoms when subsequently challenged with the offending antipsychotic. Nevertheless, it appears that individuals who have had an episode of NMS are at greater risk for recurrence.

The profound rigidity, which on occasion may resemble catatonic waxy flexibility, results in the generation of excessive heat through the hydrolysis of adenosine triphosphate (ATP) in the striate muscle, causing rabdomyolysis. Thus, hyperthermia does not appear to be a consequence of a failure of central temperature control per se as the affected patients are often quite diaphoretic. In addition, dystonia of the oral pharyngeal regions interferes with efficient clearance of secretions, which can cause complicating aspiration pneumonia. Hyperthermia and dehydration due to diaphoresis and impaired oral intake contribute to cardiovascular instability. Rabdomyolysis can also cause renal damage and failure. A peculiar and poorly understood feature of the disorder is that symptoms can persist for days to weeks after the last administration of antipsychotics. The fatality rate has been estimated to be as high as 20%.

The medically acute and uncommon occurrence of NMS has precluded carefully controlled studies of its management. Nevertheless, a review of published reports suggests that the following treatment principles may be reasonable.[32] The first, anticholinergic drugs should be avoided because they interfere with diaphoresis and thereby exacerbate the hyperthermia. Supportive care with attention to hydration and clearing of secretions is imperative. There is debate whether dantrolene, a drug that directly interferes with myosin induced ATP hydrolysis and thus heat production, is an effective agent for rapidly reducing the hyperthermia and reversing rabdomyolysis.[36] It should be remembered that some patients may have developed complicating infections due to aspiration, which may be an additional cause for fever. However, dantrolene is ineffective in treating the rigidity, delirium, and oral dystonias. Several reports suggest that bromocriptine administered in increasing doses to titrate the patient's symptoms is more effective for reversing these latter symptoms. While some have argued that bromocriptine is the primary drug of choice, the delay in attaining the optimal dose may result in unnecessary persistence of hyperthermia and rabdomyolysis, which could be rapidly controlled with dantrolene. Finally, once the patient has responded to bromocriptine treatments, the dose should be tapered gradually and cautiously, with attention paid to possible recurrence of NMS symptoms.

Antidepressants

Major Depressive Disorder

Major depressive disorder (MDD) is the most common serious psychiatric disorder, affecting up to 15% of individuals at some time in their life.[37] The risk for the MDD is similar for males and females prior to puberty, afterwards the risk for women is 2-to 3-fold greater than for males. Depression is one of the most costly illnesses to Society because of lost productivity and absenteeism as well as financial losses as a result of early death by suicide.[38] It has become apparent that MDD and subsyndromic depression (i.e., does not fulfill DSMIV criteria) is a robust predictor of poor outcomes when it occurs in the context of medical illness. For example, coexisting depression is a more powerful predictor of subsequent death in patients with myocardial infarction than EKG status.[39] Patients who develop depression after a stroke have a significantly poorer prognosis than those with no mood disturbance.[40] In the case of diabetes, concurrent depression is associated poor glycemic control and an elevated risk for vascular complications. Thus, the general clinician as well as the neurologist will frequently encounter MDD in their practice and will need to treat it in order to reduce the morbidity and mortality of their patients.

The cardinal symptoms of MDD include depressed mood, inability to experience pleasure, changes in appetite, insomnia, agitation or marked slowing of movement (retarded depression), impaired concentration and recurring thoughts of death and suicide (Table 13–3). Because the somatic symptoms often dominate the picture from the patient's perspective, the patient may not recognize that they are depressed and ascribe their depressed mood to the insomnia, agitation and sense of fatigue. This highlights the importance of including MDD in the differential diagnosis of a variety of nonspecific somatic complaints.

Table 13–3 Major Depressive Disorder

1. Five or more symptoms present for at least two weeks: depressed mood, anhedonia, weight change, sleep disturbance, psychomotor agitation or retardation, fatigue, impaired concentration, thoughts of death, or suicide
2. Symptoms cause clinically significant distress or impairment
3. Symptoms not due to a drug or a medical condition
4. Symptoms are not due to bereavement

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.[78]

The differential diagnosis of MDD includes other mood disorders such as dysthemia and especially bipolar disorder. Nearly 10% of individuals diagnosed with MDD will develop bipolar disorder. The relationship between MDD and bipolar disorder is particularly important for the onset of MDD in adolescence and early adulthood, especially if there is a family history for bipolar disorder. The onset of major depression late in life presents a significant risk for the subsequent development of dementia, both vascular dementia and Alzheimer's disease.[41]

Depression can present in a variety of ways that have treatment implications. Dysthymic disorder is a chronically depressed mood that is present on more days than not but does not fulfill the criteria for an episode of major depression. This condition, which is 2 to 3-fold more common in women than in men, has a lifetime prevalence rate of 6%. Often, this chronic sub-clinical depression, which is associated with significant morbidity, is punctuated by episodes of major depression, a condition known as double depression.[42] Depression with atypical features such increased appetite (often with a craving for sweets), increased sleep, anxiety, heightened rejection sensitivity and reverse diurnal mood variation is a form that is responsive to monoamine oxidase inhibitors if amine uptake inhibitors fail.[43] Major depression with melancholic features is a severe form characterized by marked anhedonia, worse depression in the morning, early morning awakening, psychomotor slowing or agitation, weight loss and excessive feelings of guilt. Major depressive disorder with psychotic features typically presents with a mood congruent delusions that one is evil or dead or dammed or threatened with punishment (paranoia) as well as auditory hallucinations often involving condemnatory statements and even olfactory hallucinations such as the smell of rotting flesh. Major depressive disorder with psychotic features responds best to a combined therapy of an antipsychotic with an antidepressant or in severe forms electrocon-vulsive therapy. It must be emphasized that psychosis is not diagnostic of schizophrenia and occurs frequently in mood disorders.

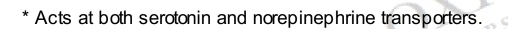
Antidepressants

The last 15 years has witnessed a remarkable increase in the number and variety of drugs used to effectively treat depression (Table 13–4). The clinical efficacy of the first generation tricyclic antidepressants (TCAs) has been demonstrated in scores of clinical trials. However, their use as first line treatments has declined dramatically even though they are much less expensive, being off patent, than many of the second-generation drugs. The major limitation of TCAs is that as little of one week's supply of medication, if ingested all at one time, can cause fatal cardiac arrhythmias.[44] This risk is of obvious concern when treating a condition in which suicidality is a frequent symptom. In addition, muscarinic receptor blocking effects can produce troubling side effects including constipation, blurry vision, and dry mouth.

Table 13–4 Second-generation Antidepressants

Generic	Therapeutic Range (mg/day)
Fluoxetine	10–80
Fluvoxamine	100–300
Mirtazepine	30–45
Nefazodone	150–300 bid
Paroxetine	20–50
Sertraline	100–200
*Venlafaxine	75–375
*Duloxetine	60–120
**Bupropion	300–450





* Acts at both serotonin and norepinephrine transporters.

** Acts at both norepinephrine and dopamine transporters.

The second-generation serotonin specific reuptake inhibitors (SSRIs) and combined serotonin and norepinephrine uptake inhibitors are not without their own limitations. While they are considerably less lethal when taken in overdose and have fewer peripheral side effects, concerns have been raised about the risk for suicide, especially during the early stages of treatment. Against this concern, one must consider the following facts. First, for over 40 years since the introduction of antidepressant treatment, clinicians have recognized an increased risk for suicide during the initial stages of treatment when the retardation and apathy resolve, permitting patients to act upon their suicidal inclinations. Second, in surveying all the clinical trials for the second-generation antidepressantsit has not been possible to identify a significant increase in completed suicides versus placebo.[45] What has been noted, however, is a two-fold increase in suicidal thoughts in the treated as compared to the placebo controls during the early stages of treatment (approximately 2% versus 1%). Suicidality is many fold more common than attempted or completed suicides, and the relationship between suicidality and suicide remains unclear. Finally, epidemiologic studies point to a reduction in suicide rates in populations with increasing use of second-generation antidepressants.[46] Unfortunately, the alarm over the suicidality issue has resulted in an FDA black box warning about suicidality and a decline in the prescription of second-generation antidepressants, especially for youth, by primary care physicians.

It is useful to consider the treatment of depression in three phases: acute, continuation and maintenance. Acute treatment refers to the initiation of therapy during the symptomatic phase of illness when diagnosis, starting drug therapy and dose titration occurs. This phase typically lasts four to eight weeks although recent studies suggest that the majority of clinical response can be noted within the first 10 days. Somatic symptoms such as sleep disorder, appetite problems, and agitation often respond more quickly to treatment than the cognitive symptoms. If the patient fails to respond on a given treatment during this period of time, then consideration of alternative treatments must

be undertaken.[47] Recent controlled trials and efficacy studies have provided algorithms for antidepressant treatment selection if the initial choice fails.[10] In the continuation phase, the patient is maintained on the effective doses of medication for a period of six to nine months. Placebos substitution trials indicate that this is a period of significant vulnerability for relapse with discontinuation of antidepressant treatment.

After the completion of the continuation period, a decision needs to be made whether a patient should be placed on maintenance treatment. For a patient with an isolated episode of MDD, antidepressants could be tapered with careful attention for recurrence of symptoms. Patients with dysthymia and recurrent depression or patients with a history of two or more previous episodes of depression should be considered for maintenance treatment of an indeterminate duration.

Side Effects of Serotonin Specific Re-Uptake Inhibitors (SSrIs)

The development of SSRIs and related antidepressants that do not bear the liabilities of the TCAs with the risk of cardiac arrhythmias, orthostatic hypotension and muscarinic receptor blocking effects including dry mouth, constipation, and urinary retention provided a much safer treatment option for the clinician. Indeed, with education about the diagnosis of depressive disorders and increased comfort with the safety of these newer medications, there has been almost a 3-fold increase in the percentage of primary care patients receiving antidepressants, primarily SSRIs for the treatment of depression. However, with broader use, as is the case with any new class of medications, new side effects become apparent. Several of these common side effects of SSRIs bear attention.

Inappropriate antidiuretic hormone secretion (IADH) typically occurs during the first weeks of SRRI treatment.[48] The symptoms are relatively nonspecific and include headache, lethargy and muscle pain progressing to delirium and obtundation with confusion. Elderly patients may be particularly vulnerable with 12%–25% developing hyponatremia as a consequence of water retention secondary to excessive vasopressin secretion.

Serotonin is an important participant in the platelet clotting process. It is not synthesized in platelets but rather is concentrated in them by the serotonin transporter.[49] Thus, a predictable consequence of SSRI treatment is the depletion of platelets' serotonin stores. A number of epidemiologic studies have demonstrated the increased risk for gastrointestinal and uterine bleeding as well as surgically associated excessive blood loss with SSRI treatment.[50] This risk is unequivocally increased by the concomitant use nonsteroidal anti-inflammatory medications as well as coumadin.

The serotonin syndrome is a potentially life threatening condition that results from over activation of the serotonin receptors.[51] The syndrome typically appears during the initiation of treatment or with escalation of the SRRI dose, but other drugs including antimigraine triptans, opiate analgesics, dextromethorphan, St. John's Wort and methylenedioxymethamphetamine (MDMA) can increase the risk of it in patients receiving SSRIs. Symptoms include increased reflexes, clonus, agitation, diaphoresis and tremor. The serotonin syndrome may be confused with neuroleptic malignant syndrome; so antipsychotic medications should be avoided. Cyproheptadine is reported to be the most effective pharmacologic treatment for the serotonin syndrome.

Discontinuation of SSRIs, especially abrupt discontinuation, can result in the serotonin discontinuation syndrome, which can affect 20%–25% of patients.[52] Symptoms include dizziness, parasthesias, insomnia, nightmares, anxiety, diarrhea and headache. Symptoms usually appear within days of decreasing or discontinuation of the SSRI and can last up to two weeks. SSRIs with long half-lives such as fluoxetine and sertraline are less frequently associated with the syndrome because blood levels decrease gradually after discontinuation.

Developmental neurobiology has now revealed a critical role of serotonin in modulating fetal brain development. As a consequence, there has been an increased concern about the use of SSRIs during pregnancy.[53] An increased risk for fetal malformations has been reported with paroxetine although meta-analysis of the teratogenic effects of SSRIs is inconclusive.[54] Recent studies have demonstrated symptoms consistent with the serotonin discontinuation syndrome in newborns of mothers, who were receiving SSRIs during the third trimester of pregnancy. Thus, antidepressants should be avoided during pregnancy, if at all possible.

Clinical Use

Because antidepressants may be prescribed for months to years, a number of factors should be considered in selecting the appropriate antidepressants including efficacy, side effects, interactions with other medications and expense. Currently, there are nearly 20 different first and second generation antidepressants available for clinical use. A practical approach for the clinician is to select a couple with differing profiles and use them regularly so as to become familiar with their therapeutic profile.

The TCAs as a class have repeatedly been demonstrated to be efficacious in clinical trials over the last 40 years. The tertiary TCAs such as amitriptyline, imipramine, and doxepin are potent serotonin uptake inhibitors whereas the secondary amine TCAs such as nortriptyline, desipramine, and desmethyldoxepine (a metabolite doxepine) are potent norepinephrine uptake inhibitors. The major disadvantage of the TCAs is their side effects. Histamine H1 receptor blocking activity is associated with significant sedation although this will usually decrease with continuous use. Blockade of alpha noradrenergic receptors can cause orthostatic hypotension, a substantial risk for the elderly because of falls. Muscarinic receptor blockade can cause tachycardia, constipation and confusion, especially in the elderly or cognitively compromised. The risk of fatal cardiac arrhythmias with overdose of the TCAs is a major limitation. Thus, currently TCAs continue to have a role in the treatment of major depression although not as first choice medications.

At the present time, the serotonin reuptake inhibitors are the primary pharmacologic treatment for depression. Although all SSRIs appear to act by the same fundamental mechanism, they do exhibit differences in side effects, pharmacokinetics, and potential drug interactions. More recently, the FDA approved duloxetine and venlafaxine, which inhibit both the norepinephrine and serotonin transporters but the latter more potently. Surprisingly, a recent large-scale effectiveness trial indicated that if a patient fails on one SSRI they can still respond if another SSRI is substituted.[10]

The prototypic SSRI is fluoxetine, one of the first psychotropic medications developed against a specific molecular target, that is, the serotonin transporter. Fluoxetine has several advantages. Being off patent, it is relatively inexpensive. It has a long half-life of 4–6 days after chronic administration, which reduces the risk of the withdrawal syndrome. It has none of the cardiovascular side effects associated with the TCAs. On the initiation of treatment some patients can feel activated, and akathisia can occur in a small percentage of patients, which appears to be a class effect for the SRRIs.[55]

Sexual side effects are common with the SRRIs, especially with female patients. Particularly troublesome are delayed orgasm or anorgasmia as well as decreased libido. Several strategies have been proposed to deal with this side effect including reducing the dose, changing to an SSRI with a short half life such as paroxetine coupled with drug holidays or coadministration of buspirone, amantidine or bupropion. Table 13–4 lists the commonly used SSRIs, the adult dosage ranges and half lives.

Patients with their first episode of major depression should be treated for 6–12 months after they have recovered from their episode. Discontinuation prior to this is associated with a significant chance for relapse, even though the patient may be asymptomatic. To minimize a withdrawal syndrome, the medication should be tapered over 1–2 months with careful attention to the possible recurrence of symptoms.[56] Patients with a history of three or more episodes of major depression should continue on the effective antidepressant for the foreseeable future.

Loss of efficacy with maintenance treatment can be a problem with the SSRIs. Blier has argued on the basis of electrophysiologic studies that this may result from enhanced inhibition of locus coeruleus noradrenergic neuronal activity.[57] The results of double-blind studies suggest that adding the norepinephrine inhibitor desipramine or the catecholamine releaser bupropion can augment response. Alternatively, high dose venlafaxine, which effectively blocks both norepinephrine and serotonin transport, or the combined inhibitor duloxetine might be a reasonable substitution.

Cognitive-Behavioral Therapy (CBT)

Psychologic interventions can also have robust therapeutic effects in depression. The best studied is CBT, a manualized psychologic intervention that reenforces positive

thinking. Controlled clinical trials, like those to which drugs are subjected, have shown its efficacy in treating depression.[58,59] Furthermore, combining CBT with antidepressant treatment can hasten the onset of symptom reduction and reduce rates of relapse in patients with depression.[60] Referral for CBT should be considered for patients, who are unwilling to take antidepressants (because of sexual side effects, for example) or should avoid them (pregnancy).

Mood stabilizers

Bipolar Affective Disorder

Biopolar affective disorder (BPAD) is a quite disabling mood disorder characterized by episodes of depression and episodes of mania or hypomania interspersed between periods of relatively normal mood. It has also been known as manic-depressive illness. As depression is the most prominent and disabling component of the disorder, suspicion for BPAD should be high in individuals with recurrent episodes of depression, especially if they have a positive family history for BPAD. The distinction between major depressive disorder and BPAD is not trivial because of important differences in treatment. Bipolar I disorder, which is characterized by episodes of mania (Table 13–5) and episodes of depression, affects approximately 1% of the population. Bipolar II disorder is characterized by recurrent episodes of depression and episodes of hypomania and affects over 2% of adults. Hypomania is generally not dysphoric because it is associated with feeling upbeat, energetic and optimistic. Thus, bipolar II may be more difficult to diagnose because patients do not recognize the hypomanic period as dysfunctional. An important feature of BPAD is the remarkably high risk for comorbid substance abuse and dependence, which can be 4- to 10-fold greater than in the general population. Substance abuse is an important issue to address because it adversely affects outcome.[61]

Table 13–5 Manic Episode

1. Elevated, expansive, or irritable mood persisting for more than one week
2. Three or more symptoms: Grandiosity, reduced need for sleep, very talkative, racing thoughts, distractibility, increased goal directed activities, excessive involvement in pleasurable activities
3. Marked impairment in occupational functioning
4. Not due to a drug or a medical condition

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, 4th ed.[78]

The heritability of bipolar disorder is high (0.7). Linkage and association studies indicate that bipolar disorder is a disorder of complex genetics with multiple genes of modest effects interacting to produce the phenotype.[62] Several putative risk genes have been identified and some of these such as *G72* and *DISC1* are also associated with increased risk for schizophrenia. As episodes of mood disturbance in bipolar disorder often synchronize with the seasons and within episodes there is clear evidence of disruption of circadian rhythms, there has long been speculation that it may be a disorder of the circadian clock. Recent studies have implicated circadian clock genes in BPAD and comorbid substance abuse.[63]

Clinical Use

The effective treatment of bipolar disorder must address two issues: the management of the presenting mood disturbance and the prevention of recurrence of subsequent episodes. Atypical antipsychotic drugs including risperidone, olanzapine, and ziprasidone are particularly effective in treating acute manic psychosis although mood stabilizers are generally started at the same time. With regard to depressive episodes, SSRIs are generally used along with a mood stabilizer. Lithium, valproic acid, and lamotrigine are the most commonly used mood stabilizers and are administered chronically after resolution of the acute mood disturbance to diminish the risk of occurrence of subsequent episodes.

Lithium (Li+) was first introduced to treat mania by the Australian psychiatrist John Cade in 1949. The ability of lithium to prevent the recurrence of episodes of mania and depression was convincingly demonstrated by the Danish psychiatrist Mogans Schou. Lithium was finally approved by the FDA in 1970 for use in bipolar disorder. Patients with typical bipolar I tend to be good responders to lithium whereas those with mixed manic states or rapid cycling respond much less well.[64] Comorbid substance abuse also predicts a poor response to mood stabilizers.

In spite of its poor therapeutic index (toxic blood levels are twice the therapeutic levels), lithium is relatively well tolerated. Lithium is available as a salt, as a controlled release formulation, a slow release formulation and a syrup. The half-life of lithium is between 18 and 24 hours, and it is eliminated exclusively by the kidney. For adults, treatment is often begun at 600 to 1200 mg/day in divided doses. Therapeutic serum levels are between 0.8 and 1.2 meq/L. Serum levels should be measured every several days until steady therapeutic levels have been achieved. After stable therapeutic serum levels have been established, serum levels should be measured every six months unless there is a change in clinical status or the emergence of lithium related toxic side effects.

Lithium toxicity may occur even within therapeutic serum levels of lithium, especially in vulnerable individuals such as the elderly. Early symptoms of lithium toxicity include a course tremor, ataxia and dysarthria. Increasing levels produce more serious symptoms including confusion, fasiculations, myoclonus, coma and death. Factors that increase the risk for development of toxicity are excessive intake of lithium, reduced intake of sodium and conditions that cause dehydration such as vomiting and diarrhea.

Valproic acid was demonstrated in clinical trials to be as effective as lithium and more effective than placebo in treating acute mania.[65] Subsequent studies suggested that it is as effective as lithium in maintenance treatment to prevent recurrence of episodes.[66] But like lithium, it appears more efficacious against manic episodes as compared to depressive episodes.

Valproic acid is generally administered in enteric-coated preparation of divalproex sodium (Depakote). Starting doses are typically between 500 to 1000 mg/day for an adult, administered in divided doses. Serum levels must be monitored frequently during initiation of treatment at the 12-hour trough. The therapeutic concentration is between 50 and 120 μg/ml. Valproic acid is generally well tolerated although gastrointestinal symptoms, mild elevations of hepatic transaminases and sedation can occur during the initial stages of treatment. After the patient is stabilized, regular monitoring of hematologic indices including platelets and liver function tests should be done.

Lamotrigine, a newer generation antiepileptic, has also been demonstrated in placebo controlled clinical trials to prevent the recurrence of mood episodes in BPAD.[67] Of particular interest is the fact that it appears to be more efficacious in treating recurrent depressive episodes than either lithium or valproic acid.[68] It exerts its anticonvulsant effects by inhibiting voltage-gated ion channels,[69] although inhibition of GSK3β may be a common site of action for lamotrigine, lithium and valproic acid.[70] The therapeutic dose range for maintenance treatment in BPAD is between 100 and 400 mg/day, which is achieved by dose escalation of 25–50 mg/week with a starting dose of 50 mg. The most common side effect of concern is skin rashes, which occur in approximately 10% of patients receiving lamotrigine with the risk of Stevens-Johnson syndrome being 0.1%.

Benzodiazepines

While benzodiazepines are among the most frequently prescribed psychotropic medications, there use for purely psychiatric indications is rather limited. Benzodiazepines are commonly prescribed to reduce anxiety, which may be related to situational life stress. However, severe chronic anxiety disorders including panic disorder, generalized anxiety disorder, and posttraumatic stress disorder are more appropriately treated with a combination of psychological interventions and SSRIs.[71] In these conditions, the use of

benzodiazepines poses the risk of dependency and abuse with minimal long-term therapeutic effects. The benzodiazepines have supplanted the previously used anxiolytics such as the barbiturates, which have a poor toxic to therapeutic ratio and a greater reliability for physical dependence. A substantial number of benzodiazepines are available for prescription use, which differ with regard to potency, metabolic characteristics and half-lives. They all appear to act through a common mechanism.

Receptor-ligand binding techniques, patch clamping electrophysiologic studies, immunologic studies, and molecular biologic strategies have clarified the mechanism of action of the benzodiazepines and related sedatives and anticonvulsants of the barbiturate class.[72] The GABA-A receptor is a macromolecular complex consisting of subunits derived from seven gene families totaling 18 distinct subunits that form the GABA-gated chloride channel. However, three subunits (α, β, and γ) are the most prevalent, and the α-subunit family has the benzodiazepine binding site. Site-directed mutagenesis has revealed heterogeneity of the benzodiazepine sites among the different α-subunits. These studies indicate that the α_1 containing receptors, which represent 60% of the synaptic and extra-synaptic GABA-A receptors, mediate sedative and anticonvulsant effects whereas site-directed mutagenesis has demonstrated that the α_2 containing receptors mediate the anxiolytic effects of benzodiazepines. GABA-A receptors containing the α_2 subunit are the major form expressed in the central nucleus of the amygdala, a key structure involved in anxiety.[73]

Overdoses of benzodiazepines alone are associated with a low risk of respiratory arrest and death. However, if they are taken in combination with ethanol or barbiturates, the toxic effects of the latter agents can be markedly potentiated. The positive interaction between barbiturates, which act at the chloride ionophore, and benzodiazepines can be readily understood by their cooperative molecular sites of action. Ethanol is an allosteric enhancer of GABAergic neurotransmission at the receptor level thus the combined effects in terms of profound inhibition is apparent.[74]

Increasingly, for sleep promotion, benzodiazepines are being supplanted by nonbezodi azepine soporifics that act selectively at the α-1 GABA-A receptor benzodiazepine site including zolpidem, zapelon, zopiiclone, and eszopiclone.[75] In placebo-controlled studies, these drugs have been shown to improve sleep latency and sleep quality. The absence of interactions with α-2 GABA-A subunit reduces the risk for abuse and dependency. An advantage of zaleplon in comparison to the others is that it is not primarily metabolized by cytochrome P450 3A4.

As benzodiazepines are commonly used as soporifics, there has been increasing concern about dissociative effects associated with benzodiazepines and the nonbezodiazepine hypnoyics like zopiclone, especially in combination with alcohol or other sedatives. Individuals affected by the dissociative syndrome can engage in complex activities such as driving their automobiles, eating binges or other social interactions for which they subsequently have no recall.

In spite of the clinical superiority of benzodiazepines over older sedative/anxiolytics, medical experience dictates cautious use of them to treat anxiety symptoms in patients. First, while they can be quite helpful in reducing stress related anxiety in patients, the chronically anxious patient is at risk for dependency due to prolonged use. Furthermore, while reductions of severe anxiety may be quite helpful, especially in the context of acutely distressful situations, when anxiety is recurrent it appears to be related to a more persistent anxiety disorder. The continuous use of benzodiazepines may deter the patient from addressing more directly these conflicts through psychological treatments. Of course such anxiety should be distinguished from panic disorder, which is neither particularly responsive to benzodiazepines nor clearly related to psychological conflicts.[76] Second, it is now clear that chronic administration of benzodiazepines can result in both psychological and physiologic dependence. In the case of the longer acting benzodiazepines, acute withdrawal can result in delayed recurrence of anxiety symptoms, jitteriness, insomnia, and on occasion seizures. However, the short acting benzodiazepines such as alprazolam when administered continuously, are associated with marked propensity for seizures and profound anxiety symptoms upon acute withdrawal.[77]

Conclusion

Basic neuropsychopharmacologic research has clarified the molecular sites of action of the major classes of psychotropic medications. These advances have contributed substantively to our understanding of their mechanisms of action at the cellular level, and brain imaging studies have illuminated their effects at the neural systems level. However, with the exception of the recent identification of antiepileptic mood stabilizers, treatment of common, serious psychiatric disorders has been hampered by the failure to introduce antipsychotic or antidepressant medications that act by truly novel mechanisms. The need is substantial as most individuals with schizophrenia remain seriously disabled for life and a third of patients with mood disorders show only partial response to current therapies. The accelerating advances in psychiatric genetics hold the promise that with the identification of risk genes for serious psychiatric disorders the underlying pathologic processes will be better understood, thereby leading to rational drug development to target causes and just symptoms. Furthermore, it is likely drugs will be introduced that address components of disorders such as cognition in schizophrenia, which are inadequately treated with current drugs.

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Childhood Cognitive Disorders

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Cognitive disorders are common causes of disability in children, with medications such as stimulants widely used to improve attention, behavior, and learning. The spectrum of childhood cognitive disorders ranges from the lower-prevalence, higher-severity disorder of intellectual disability (ID; also commonly referred to as mental retardation, global developmental delay, or learning disability [United Kingdom]) to the high-prevalence, lower severity learning disabilities (LD) including reading disorder (RD; developmental dyslexia) and attention-deficit hyperactivity disorder (ADHD).

The overall prevalence of developmental disabilities is estimated at 17%,! based on the 1988 National Health Interview Survey (NHIS), with 6.5% reporting LD. Estimates of the prevalence of ID place its prevalence at approximately 1% of school-aged children.[2] Approximately 8 per 1,000 children have mild ID (IQ 50–70), while 4 per 1,000 have severe ID (IQ <50). Down syndrome (DS) is among the most common causes of ID and is the most common of the major birth defects, with its prevalence estimated at 13 per 10,000 live births.[3] With the common overlap between LD and ADHD, the Centers for Disease Control and Prevention (CDC) investigated the prevalence of each of these disorders in the 1997–1998 NHIS, finding 2.6 million children 6 to 11 years of age affected. Three percent of children in this age group were diagnosed with ADD alone, 4% with only LD, and 4% with both.[4]

Mental retardation is currently defined by the American Association on Intellectual and Developmental Disabilities (formerly American Association on Mental Retardation [AAMR]) as “a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. This disability originates before the age of 18.”[5] (p8) The American Psychiatric Association (APA) has also defined this disability similarly in its *Diagnostic and Statistical Manual (DSM-IV)*, with three coexisting features: (1) significantly subaverage intellectual functioning accompanied by (2) deficits or impairments in adaptive functioning that are (3) evident before age 18.[6] Intelligence quotient-based subcategories are no longer used in the AAMR definition but are provided in the *DSM-IV* as well as by the World Health Organization,[7,8] ranging from mild to moderate, severe, and profound. In mild ID, IQ is 2 to 3 SD below the mean (50–55 to 70); in moderate ID, IQ is 3 to 4 SD below the mean (35–40 to 50–55); in severe ID, IQ is 4 to 5 SD below the mean (20–25 to 35–40); and in profound ID, IQ is more than 5 SD below the mean (below 20–25). Epidemiologic studies often subdivide it into mild (50–70) and severe (below 50) alone. The AAMR definition instead uses multiple dimensions for further description, including intellectual abilities, adaptive behaviors, participation, interactions, social roles, physical and mental health, and environmental and cultural context.

The definition of a specific learning disability is currently incorporated in the United States Individual with Disabilities Education Act as “a disorder in one or more of the basic psychological processes involved in understanding or in using language, spoken or written, that may manifest itself in an imperfect ability to listen, think, speak, read, write, spell, or do mathematical calculations” and “includes such conditions as perceptual disabilities, brain injury, minimal brain dysfunction, dyslexia, and developmental aphasia.”[9](p118 STAT. 2657–2658) It specifically excludes children who have learning problems resulting from primary visual, hearing, or motor disabilities, mental retardation and environmental, cultural, or economic disadvantage. The APA uses the term *learning disorder* with a more applied definition, “when the individual’s achievement on individually administered, standardized tests in reading, mathematics, or written expression is substantially below that expected for age, schooling, and level of intelligence. The learning problems significantly interfere with academic achievement or activities of daily living that require reading, mathematical, or writing skills.”[6] (p49) They subdivide LD into reading disorder, mathematics disorder, disorder of written expression, and learning disorders not otherwise specified. Most research on learning disabilities has been centered on RD. Lyon, Shaywitz, and Shaywitz have characterized RD or dyslexia as “difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities,” which “typically result from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction.”[10] (p2)

Mechanisms of cognitive disorders in children

The cognitive disorders represent a heterogeneous group of conditions with multiple etiologies. In those most severely affected, those with severe ID, a cause may be

determined in less than half of cases, with genetic causes, the most common of these being Down syndrome (16.5%), perinatal conditions (10.7%), postnatal events (7.3%), and teratogens (4.9%; congenital infections, alcohol) in the 1985–1987 CDC sample.[11] Biomedical etiologies account for even fewer of the cases of children with mild ID, with 87% having no defined cause. In this group, 7.3 % were of genetic origin, with Down syndrome again being the most common cause, 3.9% perinatal, 2.2% postnatal, and 2.2% teratogenic. Other less common causes for mental retardation include central nervous system defects, such as CNS malformations and disruptions, as well as other birth defects, such as hypothyroidism, CHARGE association, and Pierre Robin anomaly. In the less severe learning disorders, multiple etiologies have also been recognized,[12] including genetic disorders (e.g., neurofibromatosis type 1),[13,14] chromosomal disorders (e.g., fragile X syndrome,[15] velocardiofacial syndrome),[16,17] perinatal conditions, including prematurity,[18] intrauterine exposures (e.g., alcohol[19]), and environmental exposures (e.g., lead).[20] The frequency of such conditions amongst children with learning disorders has not been established. However, in RD, a strong genetic basis has been established on the basis of family and twin studies,[21] with approximately 50% of problems in performance accounted for by heritable factors.[22] Environmental influences appear to be greater in children with lower IQ scores.[23] Genetic linkage analyses have implicated loci on chromosome 2, 3, 6, 15, and 18,[24] with four candidate susceptibility genes *(DYX1C1, KIAA0319, DCDC2, ROB01)* that are involved in neuronal migration and axon growth.[25]

Neuroanatomic findings in children with mental retardation center on abnormalities of cortical development and include a wide range of defects including malformations, abnormalities in neuronal circuitry, and defects affecting synaptic transmission (Table 14–1).[26] A large number of genes and their associated proteins have been implicated in these processes, affecti ng cellular activities such as division, protein-coupling, transcription, vesicle and membrane trafficking, microtubular functioning, peroxisome assembly, glycosylation of the extracellular matrix, and synapse formation and maintenance.[26,27] Specific gene mutations affecting the signaling pathways and transcription factors have been identified in Coffin Lowry syndrome, Rubenstein-Taybi syndrome, Rett syndrome, neurofibromatosis type I, tuberous sclerosis type 2, lead poisoning, hypothyroidism, and other causes of severe mental retardation.[27]

Table 14–1 Classification of Disorders of Cortical Development in Cognitive Disorders[26]

Class and name of disorder:

- Proliferation and neuronal generation
  - Microcephaly
  - MSGP
  - Microlissencephaly
- Proliferation and patterning
- o Polymicrogyria
  - Schizencephaly
- Neuronal migration
  - Periventricular heterotopias
  - Type I Lissencephaly
  - Pachygyria
  - Zellweger syndrome
- Extracellular matrix integrity/glycosylation
  - Type II Lissencephaly
- Connectivity
  - Autism, mental retardation, other cognitive disorders?



Those affected with DS have brains that are small, rounded, and foreshortened, with diminished and malformed growth of the frontal and temporal lobes due to impaired neuronal differentiation.[28] Histologic changes include abnormalities in cortical lamination, irregular clustering of neuronal cell bodies, muted dendritic arborization, and proliferation of dystrophic neurites.[28] In addition, adults with DS develop early senile plaques, beta amyloid deposits, and neurofibrillary tangles like those seen in Alzheimer's disease (AD) by their fourth decade of life.[28,29] Given that the etiology of DS is trisomy of chromosome 21, the neuropatho logic changes seen in DS have been assumed to be related to the overexpression of genes on this chromosome, but other genes have also been implicated. The molecular genetic abnormalities seen are believed to lead to proteins causing apoptosis, abnormal transcription, and reactive oxygen species, causing the brain abnormalities observed.[28] There appears to be a role for cholesterol, apolipoprotein E, and inflammation in the later AD-like changes seen in DS.[29]

In LD, neuropathological findings seen include ectopias in cortical layer 1, focal microgyria, and defects in the thalamus and cerebellum.[25] Differences have been described in the temporal, parietal, and occipital brain regions between those with RD and controls, based on postmortem findings, brain morphometry, and diffusion tensor magnetic resonance imaging (MRI).[30] As noted above, the dyslexia susceptibility genes identified, *DYX1C1, KIAA0319, DCDC2, ROB01*, may account for the cortical abnormalities. Through their effect on neuronal migration and axon growth, abnormal circuitry between cortical areas and the cortex and thalamus may develop and account for the sensory, motor, perceptual, and cognitive problems seen in LD, including the phonologic deficits, motor deficits, and problems in auditory discrimination that are more specific to RD.[25]

The learning problems in RD have been correlated with the anatomic findings in recent functional imaging studies.[30] In comparing dyslexic readers and controls during nonword rhyming, disruptions have been identified in the posterior region involving the superior temporal gyrus and angular gyrus and increased activation in the anterior region of the inferior frontal gyrus. Those with RD have also been found to have decreased activation in both left hemisphere and right hemisphere sites in the frontal, temporal, parietal, and occipital areas during phonologic analysis tasks.[30] Shaywitz and colleagues have suggested that two types of RD may be distinguishable by functional MRI. Persistently poor readers (PPR) may be predominantly genetic in origin while accuracy improved readers (AIR) may be more environmentally influenced. Similar patterns have been identified in activation patterns on pseudo-word rhyming tasks, but differences noted on real word reading, with AIR using more ancillary systems in reading than PPR. They also describe "a neurobiological signature for dyslexia,"[30] (p1307) with a disruption of left hemisphere brain systems in RD during reading performance. They suggest that affected children attempt to compensate by shifting to anterior ancillary systems involved in articulation, assisting in sound awareness, and right hemisphere systems involved in other perceptual processes, resulting in slower nonautomatic reading, and recommending a potential neurobiologic target for skilled reading in the left occipitotemporal word form area.[30]

Drugs and their mechanisms of action

Pharmacotherapy in children with cognitive disorders has been centered primarily on the stimulant medications and other drugs targeting attention and related executive

function, and, as such, treats the commonly associated ADHD. Another class of medications, the nootropics (derived from the Greek *noos* for mind and *tropein* for towards), has more recently been used in adults with dementia, and is more specifically aimed at improving cognitive abilities. The use of nootropic agents in children has primarily been used in children with Down syndrome.

Attention-Targeted Medications

The era of the pharmacologic treatment of childhood cognitive disorders began with the development of the amphetamines Benzedrine and Dexedrine and the discovery of their ability to affect attention and hyperactivity in 1937. With the development and marketing of methylphenidate as Ritalin in 1955, a large expansion of the use of these agents began. Atomoxetine, a selective norepinephrine reuptake inhibitor, was developed in 1983, and was found effective in improving attention-related learning and behavior with its first trials in adults with ADHD in 1998 and children in 2001. The stimulant medications and atomoxetine are the mainstay of medical management of attention-related problems through the present day. The alpha agonists clonidine and guanfacine are less commonly used alone in the treatment of attentional problems but are often used in combination with a stimulant medication or atomoxetine (Table 14–2).

Table 14–2 Medications Used in the Treatment of ADHD

Medication	Class	Dose*	Daily Frequency	Side EffectS
Amphetamine	Stimulant	0.3–1.5mg/kg/day		
Short-acting (Dexedrine tabletstt) Intermediate-acting (Adderall, t Dexedrine spansules††) Long-acting (Adderall-XR)t			Two-three Once Once	*Common to all stimulants:* Insomnia Anorexia Tic exacerbation Mood change *Preparation Specific:*
Methylphenidate Short-acting (Ritalin,† Metadate,† Focalin,†† Methylin†) Long-acting (Concertat, Ritalin LA†, Metadate CD†, Focalin XR††) Transdermal patch (Daytrana†)	Stimulant	0.5–2.0mg/kg/day	Once Two to four Once Once	Rebound phenomena (more common with short-acting preparations)
Clonidine (Catapres)	Antihypertensive	3–10 mcg/kg/day	Two to four	*Common to antihypertensives* Sedation (less with guanfacine) Dry mouth Depression
***Guanfacine* (Tenex)**	Antihypertensive	30–100 mcg/kg/day	Twice	Hypotension (including orthostatic) and associated symptoms of lightheadedness, dizziness
Atomoxetine (Strattera)	Selective Norepinephrine Reuptake Inhibitor	0.5–1.4mg/kg/day	One to two	Abdominal pain, nausea/vomiting constipation, dry mouth Appetite suppression Liver toxicity (rare)
Tricyclic Antipressants*	Antidepressant		One to two	Dry mouth Constipation
Imipramine (Tofranil)		2.0–5.0 mg/kg/day		Weight change EKG changes
Nortryptiline (Pamelor)		1.0–3.0 mg/kg/day		
Bupropion Short-acting (Wellbutrin) Long-acting (Wellbutrin SR)	Antidepressant	1.0–6.0 mg/kg/day	Three Once	Irritability, insomnia Lower seizure threshold Contraindicated in bulimia

* Recommended doses by weight (mg/kg/day) intended as a guide. Optimal dose varies by patient. Medications may have maximum doses recommended by the manufacturer. Slow titration is recommended to achieve a dose that provides maximal benefit with minimal side effects.

** Monitoring blood levels useful in guiding tricyclic antidepressant dosing.

† Mixed salt (dextro + levo forms)

†† Dextro form only.

Parentheses indicate trade name

Approximately two million children in the United States are currently receiving prescriptions for the stimulant medications, methylphenidate and the amphetamines, with approximately 2%–5% of school-aged boys receiving such treatment.[31–34] These medications affect the dopaminergic and noradrenergic systems in the frontal cortex by raising extracellular levels of dopamine (DA) and norepinephrine (NE), specifically affecting the dopamine transporter (DAT) and norepinephrine transporter (NET) and blocking reuptake of DA and NE.[35–37] The amphetamines additionally enhance the release of DA and NE at the synaptic cleft. Methylphenidate and the amphetamines also decrease the catabolism of DAT and NET through the inhibition of monoamine oxidase. Each exerts its effect on the prefrontal cortex, the striatum, and the nuclear acumbens.

The selective norepinephrine reuptake inhibitor atomoxetine acts more selectively on the NET, blocking reuptake of this neurotransmitter, with animal studies showing effects

on the prefrontal cortex alone. The alpha agonists exert their effect on the noradrenergic system of the prefrontal cortex through the stimulation of presynaptic and postsynaptic alpha-2 receptors. While the effects of each medication on specific neurotransmitters and specific loci in the brain are known, medication choice is typically centered on clinical efficacy data, onset of action, and duration of effect, with no clear advantage established in the specific targeting of the DAT or NET.

Stimulant Medications

Methylphenidate is a piperazine-substituted phenylisopropylamine currently available as a racemic mixture of threo diastereomers (DL-threo-methylphenidate; Ritalin, Concerta, Metadate, Methylin, Daytrana) or as the D-threo-enantiomer (D-threo-methylphenidate; Focalin). The pharmacologic activity is derived primarily from the D-isomer (Table 14–2). It is rapidly absorbed and achieves maximum plasma concentration one to three hours after oral administration. It is rapidly metabolized and excreted in the urine as the inactive compound ritalinic acid, with a half-life of approximately three hours. There is a wide range of bioavailability in children from 11% to 53%, accounting for the variability in both measured plasma concentrations and in clinically effective dosing.[38,39]

Amphetamine is phenylisopropylamine (or alpha-methyl-phenylethamine) and is available as its d-isomer, dextroamphetamine (Dexedrine), or as its racemic mixture, the d,1-amphetamine salt (Adderall), with a three to one ratio of the d-and 1-forms. In the short-acting forms, peak plasma concentrations are reached approximately three hours after oral administration, and elimination half-life in children is 9–11 hours, with excretion in the urine.[40]

Both methylphenidate and amphetamine are available as tablets and capsules in short acting and long-acting forms. Methylphenidate is also available in liquid, chewable and transdermal forms. In clinical trials, both stimulant medications have onset of action within 30 to 60 minutes of ingestion. The short-acting forms reach peak clinical effect within one to two hours and maintain a total duration of effect of approximately four hours. The longer-acting preparations are provided in sustained release capsular forms, with durations of effect ranging from eight hours (methylphenidate, amphetamine) to 12 hours (OROS-methylphenidate). The transdermal methylphenidate patch has a delayed onset of action at 60 to 120 minutes after application with continuous drug delivery while the patch is maintained on the skin.[39,41]

Clinical trials extending across several decades have established the efficacy of the stimulant medications in improving behaviors and related learning problems associated with ADHD, with response rates estimated at 75%–80%.[42] Cognitive processes enhanced include the modulation of attention, alertness, vigilance, and arousal. Attention improvements include sustained attention, attentional allocation, motor response speed and organization, as well as motor inhibition. In learning tasks, improvements are seen in short-term recall, longterm memory tasks and working memory, as well as academic performance.[43–45] The behavioral effects appear longer lasting than those seen in cognition. In studies of children with ADHD and learning disorders, methylphenidate benefited the children with both ADHD and RD similarly to those with ADHD alone, while those with mathematics disability did not respond.[46,47] While most investigations have centered around children with ADHD and normal cognition, studies specific to children with ID show similar improvements in learning performance for those in the mild range.[48,49]

The dosing of methylphenidate ranges from 0.5–2.0 mg/kg/day, while that for amphetamine is lower at 0.3–1.5 mg/kg/day. Clinical titration is required on an individual case basis. Animal studies have suggested that high doses of the stimulant medication produce cognitive inflexibility in stimulating the prefrontal cortex.[50] However, clinical trials have shown beneficial effects of methylphenidate that are either linear with increasing doses up to 1.0 mg/kg or curvilinear with an asymptote at the highest doses.[43]

The most common side effects seen with use of both methylphenidate and amphetamine are anorexia, insomnia, dysphoria, emotional lability, and abdominal complaints. Cardiovascular effects are also seen, including tachycardia and elevation of blood pressure, and may be attributable to the medications' central dopaminergic effects.[51] Investigations suggest transient, reversible, and clinically insignificant elevations in pulse, systolic blood pressure, and diastolic blood pressure with the short-term use of both amphetamine and methylphenidate in children and adults.[52–56] Longer-term studies of children and adolescents treated with mixed amphetamine salts for 6 to 24 months have reached similar conclusions, with pulse increases below five beats per minute and pressure increases less than 5 mm/Hg.[52,57] However, treatment was discontinued in children for episodes of hypertension, tachycardia, and chest pain.[52] Concerns regarding such effects with long-term use of the stimulant medications in adults[53,58] has resulted in review by the U.S. Food and Drug Administration (FDA) and significant debate regarding the safety of the increased and the prolonged use of these medications.[52,53,58–64]

Facial and vocal tics may also occur in children treated with stimulant medications. However, given a known high comorbidity between ADHD and Tourette syndrome and related tic disorders, the risk posed by stimulant medication in the development of tics remains unclear.[65] There has also been long-running concern regarding the effects of stimulants on childhood growth. While there may be short-term weight loss caused by medication-related anorexia, long-term studies show no effect on weight or height due to stimulant treatment.[66]

Cases of drug-related adverse psychiatric events have also been reported, including mania, paranoia, and auditory hallucinations. With the FDA review of cardiovascular effects, cases of psychiatric events were also considered. As a result, the FDA has directed the manufacturers of ADHD medications to develop patient medication guides in order to alert patients to possible cardiovascular risks as well as adverse psychiatric symptoms associated with the medications.[67]

The long-term use of these psychoactive agents has raised public and professional concern regarding the validity of the diagnosis and later substance abuse in adolescents treated for ADHD.[68–70] Recent investigations and metaanalyses involving long-term follow-up of children with ADHD have however concluded that those treated with stimulant medications are not at increased risk for experimentation, use, dependence, or abuse of illicit substances, including alcohol, marijuana, cocaine, stimulants, hallucinogens, narcotics, and sedatives. Instead, treated children have been consistently found to have a lower risk for substance use and lower frequencies of dependence on such substances, with 1.9-to 5.8-fold reductions.[71,72]

Despite the controversies surrounding the use of stimulant medications in children, there is consensus among the professional organizations regarding the benefit of these medications in the treatment of attentional problems in children.[73–75] While adverse effects may occur with such treatment, these must be balanced as customary in clinical practice against the improvements seen in both short-term and long-term outcome of their use.

Atomoxetine and Other Medications

Atomoxetine is N-methyl-3-phenyl-3-(o-toly-loxy)-propylamine hydrochloride. Since its introduction as an alternative to the stimulant medications, this selective norepinephrine reuptake inhibitor has become increasingly used for the improvement of attention in children. After ingestion in its capsule form, Atomoxetine reaches its serum concentration peak in one to three hours. It is metabolized in the liver through the cytochrome P450 2D6 (CYP2D6) pathway and has a plasma half-life of five hours, with excretion in the urine. Up to 10% of users, however, are slow metabolizers, with the half-life extending up to 24 hours. Given its long half-life, once daily treatment is recommended, although its initial trials involved dosing at 12-hour intervals. Clinical effects may not be observed for one week or longer after initiation. Atomoxetine has proven benefit in the treatment of ADHD behavioral symptomatology.[76] While a benefit to learning has not been specifically investigated, cognitive improvement has been demonstrated on response inhibition tasks.[77,78] Treatment is recommended at doses of 1.2 to 1.4 mg/kg/ day, although initial treatment trials extended dosing up to 1.8 mg/kg/day, but effect has also been demonstrated at the lower dose of 0.5 mg/ kg/day.[79] Common side effects include drowsiness, dizziness, and fatigue, as well as various gastroenterologic symptoms, including abdominal discomfort, decreased appetite, nausea, and vomiting. Cases of liver toxicity have been reported but appear rare. No effect has been seen on tics in children with tic disorders.[80,81]

The alpha-adrenergic agonists, clonidine and guanfacine, and the antidepressants, including the tricyclic antidepressants (TCA) and bupropion,[35] have had limited investigation and a lesser role in the treatment of attention-related problems. While the alpha-2 agonists have known central effects in the frontal cortex and have been demonstrated to be effective in treating hyperactivity, impulsivity, and sleep problems in ADHD, beneficial effects on cognition have not been demonstrated[82,83] Instead, reduced alertness, sedation, memory impairment, and impaired performance have been seen.[84,85] The antidepressants may have a role in DA and NE reuptake inhibition, and trials have shown benefit in ADHD. However, they too have not been shown to improve cognition. Side effects and toxicity concerns have limited their use in attention disorders. Comparative trials with stimulant medications have also established the stimulants to be superior. See Table 14–2 for dosing and side effect information.

Nootropic Agents and Ampakines

Drugs such as piracetam (Nootropil) have been referred to as smart drugs or smart nutrients and are approved in Europe but not in the United States. Piracetam underwent trials during the 1980s in children with learning disabilities and one recent trial in children with Down syndrome. Piracetam is a derivative of the neurotransmitter γ-aminobutyric acid (GABA), and is described as an ampakine, due to its affinity for the AMPA glutamate receptor.[86,87] In rodent models, it has been found to increase acetylcholine and dopamine release, protect glutamate receptors, enhance membrane fluidity, increase blood flow, enhance corticosteroid function, and effect calcium channel functioning.[87,88] It has been described as neuroprotective and as improving neuroplasticity.[86] Early trials of piracetam involved children with RD and found conflicting results. On doses of 2–3g/day, several revealed improved single word reading, reading speed, word writing, and reading and writing abilities,[89–92] while others saw no improvements in reading.[93] No significant adverse reactions were reported. Despite some encouraging findings, it is not in general use in children with RD. Piracetam has more recently been used in children with Down syndrome despite the absence of empirical evidence of its benefit in this population, in part due to popular demand based upon television coverage. In a single study of 18 children performed in response to this demand, administration of 80–100 mg/kg/day of piracetam in three daily doses did not improve cognitive performance on measures of attention, learning, memory, perceptual abilities, executive processing, fine motor and visuomotor skills.[88] Adverse effects reported included aggression, agaitation, irritability, sexual arousal, sleep problems, and insomnia. Levetiracetam (Keppra) is another ampakine, used primarily for the treatment of seizure disorders in children. Trials of its use in children with autism have not yielded a nootropic effect.[94,95]

Cholinesterase Inhibitors

As described in Chapter 7 acetylcholinesterase inhibitors such as donepezil (Aricept) are widely used in the treatment of AD. With the recognition of an AD-like process in adults with DS, the success of donepezil in the treatment of AD has lead to trials initially in adults with DS and later in children. The limited literature on its use in adults with DS is inconclusive regarding efficacy in the treatment of associated AD-like dementia, due to small sample sizes. Reductions in deterioration in cognitive and adaptive skills, as well as a reduction in behavioral symptoms, have been reported at doses of 5 to 10 mg.[96] Adverse effects reported include fatigue, insomnia, diarrhea, nausea, dizziness, anorexia, agitation, aggression, memory loss, and incontinence in these small samples. However, the pharmacokinetics of donepezil in those with DS may differ from the general population, with higher plasma concentrations seen, suggesting that lower dosing may be preferable.[97] The use of donepezil in adults with DS without dementia at similar dosing to that used in those with dementia showed improved language function in two studies,[98,99] but no change in other areas of cognition, behavior, or caregiver ratings.[99] A single trial of this medication in seven children with DS using daily dosing of 2.5–5 mg for 16 weeks resulted in mixed results in language performance.[100] Improvement was seen in one of two measures in the areas of word structure and sentence structure. No serious adverse effects were seen.

Donepezil has also been used recently in other pediatric populations, although it is not approved for this purpose by the FDA. In older children and adolescents with pervasive developmental disorder (PDD), improvements in their core symptoms and in ADHD symptomatology were seen in dosages ranging from 2.5 to 30 mg without serious adverse events.[101] No benefit at 2.5–10 mg was seen in its use as an adjunct to the stimulant medications in children with ADHD.[102]

Rivastigmine,[96] another cholinesterase inhibitor, has also been used in children with DS, where improvements were seen in language, attention, memory, and adaptive function in a study involving eleven adolescents.[103] There have also been trials of these medications in children with autism and PDD, where gains have been reported in language,[104] memory,[105] behavior,[105–108] and the core symptoms of autism and PDD.[104,107,108]

Medication management of childhood cognitive disorders

The primary management of a childhood cognitive disorder is centered on psychoeducational interventions. These are most commonly provided through the child's school, but may also involve community psychologists, educators, and therapists. While the child's primary health care provider is not directly involved with such services, he or she can often play a key and unique role as an advocate for the child and family. The primary care provider can also create a medical home for chronic condition management for the child, assisting and coordinating the services needed to address the disability.[109,110] Practice parameters are available to guide the physician or other professional through the assessment and treatment options for cognitive disorders.[111] The diagnostic assessment should typically involve a comprehensive review of the child's health history, developmental history, and psychosocial environment, followed by the administration of standardized measures of intelligence and achievement. When language-based problems are suspected, speech and language assessment should also be included. Children with visual perceptual or graphomotor difficulties may also benefit from evaluation by an occupational therapist. It is based on these evaluations that a diagnostic determination is made and upon which the need for educational and therapy services should be based.

The physician plays another key role in the determination of the need for medication to treat the child's disability. As reviewed in this chapter, drug treatment of the childhood cognitive disorders is centered primarily on problems in attention and related hyperactivity, as seen in ADHD. Given the common association of LD and ADHD, the physician should consider both diagnoses when a child has academic underachievement or school behavior problems. While assuring that a child is properly evaluated for a LD, the physician should coincidentally collect information from school personnel to investigate for ADHD.[74,112–114] Using standardized questionnaires administered to both the school and the parent (and in the case of the adolescent, the teen as well), the physician can determine if a child meets clinical criteria for ADHD and its treatment.

While a wider array of medication treatment options now exist for attention problems, the stimulant medications remain the choice medication class for treating attention problems in healthy children.[73,75,113] Through progressive titration of dosing of the stimulant medication, most children can be successfully treated for ADHD. When stimulant medications are contraindicated, when there are significant adverse events, or when efficacy is not achieved, alternative medications such as atomoxetine or the alpha agonists should be considered. With the high margin of safety and demonstrated longterm efficacy, children can be treated throughout their childhood and into adulthood for their attention problems.

While nootropic agents are commonly used in the treatment of adult AD as well as the AD-like dementia of DS, these medications remain investigational for use in children with the more severe cognitive disorders such as ID or the related autistic disorders. No benefit has been seen in their use for children with ADHD. In both childhood DS and PDD, mixed results have been seen in the use of the ACI drugs and no benefit has been seen with use of the ampakines. Current literature suggests a possible benefit from the ACI medications in language development.

Conclusion

Pharmacotherapy for the childhood cognitive disorders such as ADHD, LD, and ID is currently centered on the dopaminergic and noradrenergic medications, amphetamine, methylphenidate, and atomoxetine, which target attention and executive function. With decades of experience in the use of the stimulant medications, their effectiveness in improving these functions as well as their general safety are well-substantiated, with practice parameters and guidelines available from both the pediatric and child and adolescent psychiatry communities.[73,74,75] While other medications are available for improving attention, the stimulants remain the first-line treatment at this time.

With the development of the antidementia medications, the cholinesterase inhibitors and ampakines in adults, similar trials have occurred for use of these medications in pediatric populations with known risk for ID, including DS and autism. The ampakines have not been found to have a proven benefit. The cholinesterase inhibitors have shown greater, although limited, benefit, with improvements noted in language function and autism symptoms in small trials.

Studies on children with cognitive disorders remain limited by small sample sizes and difficulties with study design, posing significant challenges to investigators.[115]

Current strategies in the treatment of the childhood cognitive disorders are centered around psychoeducational intervention, but may be combined with medication treatment for attentional problems. With the advances being made in our understanding of cognitive neuroscience, it is hoped that new medications aimed at further improving attention and at improving cognitive development in high-risk populations will become available in the coming decades.[81,87]

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Sleep Disorders

Chapter: Sleep Disorders
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Sleep is an essential function with which everyone can identify. Sleep deprivation is rapidly becoming one of the most important public health issues. Many people, health care providers included, are not aware of the numerous consequences of sleep deprivation, including medical, psychological and behavioral ramifications. Adverse effects of chronic sleep deprivation have been demonstrated in most organ systems in humans.

Sleep medicine, a relatively new medical discipline, is the multidisciplinary approach to the pathophysiology, diagnosis, and treatment of disorders of sleep and wakefulness. In April 2006, the Institute of Medicine described the state of the field of sleep medicine in the United States in a statement titled "Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem."[1] This comprehensive initiative reviewed the public health significance of sleep loss and sleep disorders and the gaps in research, education, and training. It also attempted to quantify the cost of sleep disorders including loss of business productivity, motor vehicle accidents, medical care, and medical consequences. The report concluded that despite the expansion in areas of research, current resources do not adequately provide appropriate patient care. Thus research and educational initiatives should increase awareness about sleep disorders in the general population, and specifically among health care professionals.

The field of sleep medicine has grown exponentially over the last few decades, and as understanding about the states of sleep and wakefulness increase, so will the number of targeted treatment options. This chapter will review the pharmacological therapies used to treat several of the more common sleep disorders.

Basic mechanisms of sleep-wake states

In recent years, major advances have been made in the elucidation of the circuitry that controls the transitions between sleep and wakefulness. Sleep is not simply a passive state, defined by the lack of wakefulness. Rather, both sleep and wakefulness are under active neuronal control. Under normal conditions, there is a balance that is mutually exclusive; one is either awake or asleep. The structures responsible for regulating transitions between states are under intricate and reciprocal control. It is the loss of these tightly controlled systems that defines some of the disorders of sleep and wakefulness, including narcolepsy and the parasomnias.

Behaviorally, sleep is characterized by a relaxed, recumbent position, with reduced tone and closed eyes. As the level of sleep deepens, the arousal threshold increases resulting in reduced responsiveness to environmental stimuli. Sleep is subdivided into nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. These divisions are based on characteristic physiological changes that are monitored during a polysomnogram (PSG) including electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), electrocardiogram (EKG), and respiratory monitoring. In 1968, Rechtschaffen and Kales[2] wrote the original consensus-based sleep scoring manual. It was not until 2007 that these criteria were reevaluated and now a new evidenced-based manual.[3]

Normal adult sleep is comprised of 4–6 cycles over the course of a nocturnal sleep period each approximately 90–120 minutes in duration. As shown in Figure **15–1**, humans enter sleep via NREM sleep, which is typically divided into light NREM stages 1 and 2 and deep NREM stages 3 and 4 collectively known as delta sleep or slow wave sleep (SWS)

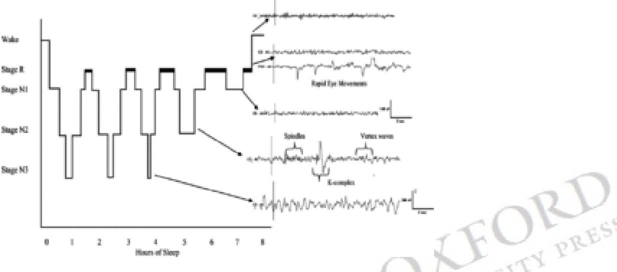


Figure 15–1.
A typical histogram over the course of one night displaying the progressive descent from wake into NREM sleep and the predominance of slow wave sleep in the first half of the night and increased duration of REM sleep in the early morning. EEG channel C3-A1 displays typical wake; Stage R with additional eye leads demonstrating rapid eye movements; increased theta of stage N1; spindles, K-complexes, and vertex waves of stage N2; and the high voltage delta waves of stage N3

Sleep onset typically begins with stage 1 sleep (or stage N1 by the new nomenclature).[4] Stage N1 is defined as the presence of slow roving eye movements, reduced but present muscle tone, slowing of the posterior dominant background, increased theta activity in the 4–7 Hz range, and the presence of vertex waves. The presence of sleep spindles and K complexes are the hallmarks stage 2 (stage N2) in the setting of low amplitude mixed frequency background. Increasing percentages of high voltage delta activity representing at least over 20% of an epoch are characteristic of slow wave sleep (stage N3). Rapid eye movement sleep, now termed Stage R sleep, is characterized by an activated state of low voltage mixed frequencies, rapid eye movements, and low chin EMG tone. Saw tooth waves in the central regions that precede bursts of rapid eye movement support this state. Rapid eye movement sleep is further subdivided into two phases: tonic REM and phasic REM. Short irregular bursts of transient muscle activity in the chin or the anterior tibial muscles in the setting of low EMG tone and bursts of eye movements characterize phasic REM (Figure **15–1**).

Wake

Wakefulness is maintained by activation of the cerebral cortex. There are a number of structures and neurotransmitter systems that promote the wake state. The brainstem reticular activating system (RAS) is the main structure that stimulates the cortex. Its two main pathways project dorsally through the thalamus and ventrally to the posterior hypothalamus. First, the pedunculopontine tegmental (PPT) and the lateral dorsal tegmental (LDT) regions in the brainstem innervate the thalamus, lateral hypothalamus and the basal forebrain. The thalamus has reciprocating thalamocortical circuits that stimulate the cortex during wakefulness also via glutaminergic systems.[5] The basal forebrain in turn stimulates the cortex through cholinergic neurons. Second, the noradrenergic neurons of the locus ceruleus (LC) and serotonergic neurons of the dorsal raphe (DR) nucleus are tonically active during wakefulness. These structures project specifically to the tubomammilary nucleus (TMN) within the posterior hypothalamus, to maintain the waking state via histaminergic neurons that project widely to the cortex.[6] This hypothalamic system is further modulated by the neuropeptide orexin (hypocretin) located primarily in the lateral and posterior hypothalamus, although receptors are found throughout the brain.[7] The PPT/LDT and LC/DT regions provide positive feedback to one another during waking and this mutual activation further promotes the wake state (Figure **15–2**).

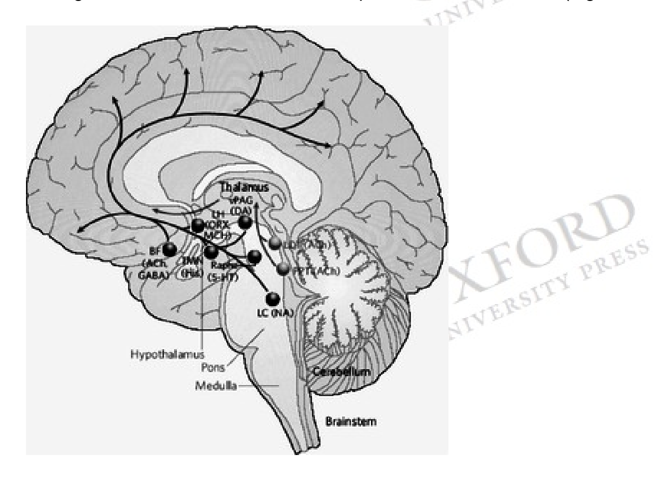




Figure 15–2.
Anatomy of the wake state. Two major pathways stimulating the cortex: (1) The cholinergic neurons of the pedunculopontine (PPT) and lateral dorsal tegmental nuclei (LDT) stimulate the thalamus which in turn stimulates the cortex through the thalomocortical circuitry. (2) The locus ceruleus (LC) via norepinephrine and the raphe nuclei via serotonin stimulate the tubomamillary nucleus (TMN) which is also modulated by the lateral hypothalamic neurons via orexin and melatonin concentrating hormone and by dopaminergic neurons of the mesocorticolimbic system (vPAG). The histaminergic neuron of the TMN stimulates the basal forebrain that are GABAergic and cholinergic in nature. Modified from Saper.[5]

Although dopamine has been recognized to be involved with behavioral arousal, its specific relationship with wakefulness is not fully understood. There are two main dopaminergic pathways within the brain. The mesocorticolimbic system arises from the midbrain and innervates the forebrain; this system may explain the action of stimulants that enhance dopaminergic transmission and the sedation associated with dopaminergic antagonists.[8] The nigrostriatal dopamine system controls the coordination of movement and the loss of these neurons is associated with Parkinson's disease and may be related to the pathophysiology of restless legs syndrome (RLS).

NREM Sleep

The anterior hypothalamus, specifically the ventral lateral preoptic (VLPO) nucleus, is responsible for signaling the onset of NREM sleep. The inhibitory neuropeptide galanin and the γ-aminobutyric acid (GABA) neurons in this nucleus inhibit the activating systems within the thalamus, cortex, and the wake promoting structures including the TMN, LC, DR, and the PPT/LDT.[9] The DR and the LC have reciprocal inhibitory feedback loops to the VLPO, such that reduction of firing reduces inhibition, further reinforcing the sleep state. The mutual inhibition between these nuclei has been called the flip-flop switch.[5]

The basal forebrain is also responsible for signaling the onset of NREM sleep. This structure is most active during wakefulness and is under tonic inhibitory control by local adenosine levels. Adenosine also inhibits other wake-promoting neurons and disinhibits the VLPO.[8] Adenosine is a byproduct of adenosine triphosphate (ATP) breakdown and accumulates with prolonged wakefulness when energy metabolism is strained. Elevated extracellular adenosine levels in the basal forebrain provide a signal for the increased

need for sleep. During sleep, adenosine levels fall as it is converted back to ATP, tipping the balance back towards wakefulness (Figure **15–3**).

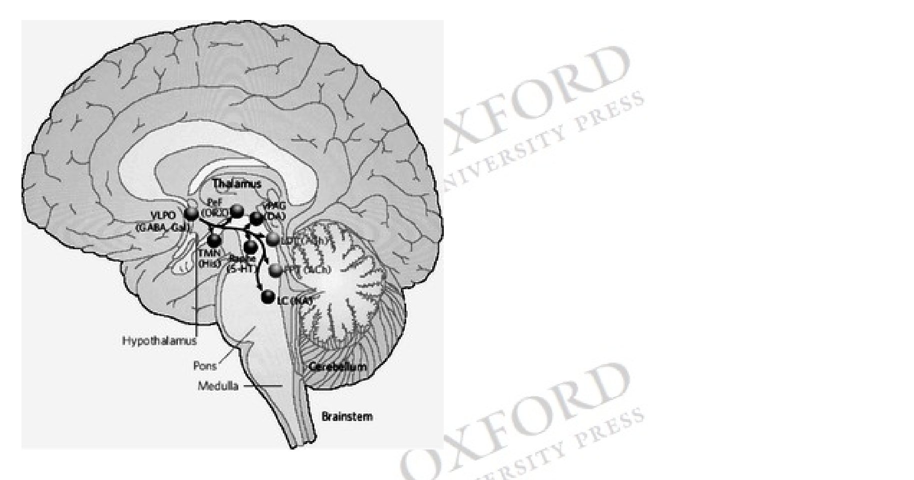


Figure 15–3.
Anatomy of NREM Sleep. The ventrolateral preoptic nucleus sends descending inhibitory galanin and GABA projections to nuclei responsible for the reticular activating system including the perifornical fibers (PeF), the tubomammilary nucleus (TMN), mesocorticolimbic system (vPAG), raphe nuclei, locus ceruleus (LC), lateral dorsal tegmentum (LDT), and the pedunculopontine tegmentum (PPT). Modified from Saper, C.[5]

The neurotransmitters that are targets for pharmacological manipulation to promote wakefulness or induce sleep include glutamate, acetylcholine, norepinephrine, serotonin, histamine, orexin (hypocretin), dopamine, GABA, and adenosine.

REM Sleep

Rapid eye movement sleep is a state of physiological activation, characterized by rapid eye movements, muscle atonia, irregular respirations, heart rate variability, penile tumescence, or labial engorgement due to increased sympathetic tone. Approximately 80% of subjects when awakened from REM sleep report dreams as compared to 20% of subjects when awakened from NREM sleep.[5] Memory consolidation appears to be one of the important functions of REM sleep.

Based on transection and lesionectomy studies, the control and regulation of entry into REM sleep resides within the PPT and LDT.[7] These cholinergic neurons project anteriorly and activate many of the same structures that were maximally active during wakefulness: the cortex, thalamus, hippocampus, brainstem nuclei, and the basal forebrain. In contrast to the wake state, the aminergic neurons of the LC and DR are at their lowest firing pattern during REM sleep. These neurons have inhibitory projections to the PPT and the LDT, therefore these structures become disinhibited.Reciprocal inhibition between the LC/DR and the PPT/LDT occurs in REM sleep, representing another flip-flop switch.

Prior to the onset of REM sleep, a volley of neuronal firing can be recorded from the pons to the lateral geniculate and then to the occipital cortex. These ponogeniculo-occipital (PGO) spikes are thought to be related to the visual imagery of dreams. The muscle atonia characteristic of REM sleep is a protective mechanism, preventing dream enactment. Neurons surrounding the PPT and LDT project caudally via the bulbar reticular formation inhibiting spinal cord α-motor neurons via the neurotransmitter glycine.[7] As a result the neuronal control of the appendicular muscles is inhibited and prevents movement, except for a few axial muscles, specifically the diaphragm, sphincters, and eye muscles, which continue to function normally.

Circadian Influences

The sleep-wake cycle is under the control of two balanced systems: the homeostatic sleep drive (the circuits have already been described), which regulates the onset of sleep based on physiological need and the duration of wakefulness, and circadian influences, which controls the appropriate timing of sleep and wakefulness. This intrinsic circadian regulation resides within the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus. The SCN coordinates external and endocrinologic cues to maintain a circadian schedule.[5,9] In a free running system, during which subjects are not given any environmental cues, either light or behavioral, the intrinsic period for the sleep wake cycle is actually closer to 24.2 hours than 24 hours.[10] As a result their sleep periods progressively delay as days pass. The body responds to external cues called *zeitgeibers* to entrain the system to the 24-hour cycle. The strongest of these cues is light. The retina is the primary sense organ that receives the light signal and projects to the SCN via the retinal hypothalamic tract. The SCN is most active during waking hours and has both excitatory projections to the LC and inhibitory projections to the VLPO to reinforce the wake state.

Melatonin is a hormone that has a circadian rhythm and participates in the regulation of the timing of sleep. It is released from the pineal gland as the light becomes dim, dim light melatonin onset (DLMO), and reaches maximal concentration between 3:00 and 4:00 *am*. Its secretion is inhibited by light. Melatonin binds to the melatonin receptors in the SCN (MT1-specific for sleep initiation and MT2-specific for maintenance of circadian rhythms) and suppresses the firing of the SCN thus shifting the balance towards sleep.[5] It also circulates systemically and may influence other organ systems.

In addition to the pathways that control the timing, the entry, and the termination of each state, there are other neuromodulators that influence all the systems discussed by either enhancing or reducing their impact. Examples include substance P, vasoactive intestinal peptide (VIP), neurotensin, corticotropin releasing factor, thyrotropin releasing factor, and various cytokines. Their specific relationship to sleep remains under investigation.[5]

There are numerous points in the brain circuitry involved in sleep and wakefulness at which aberration in normal physiology can lead to clinical disorders. Currently available pharmacologic therapies aim to enhance normal physiological systems to promote a desired state.

Drugs

Sleep-Inducing Drugs (Hypnotics)

The attributes of an ideal hypnotic includes having rapid onset to promote sleep onset, half life sufficient to maintain sleep for the desired sleep period, long term safety, and no adverse effects, tolerance, rebound, or withdrawal in all populations including the elderly.[11] The FDA currently has approved 10 agents for insomnia. These hypnotics fall into three categories based on their mechanism of action: benzodiazepines, benzodiazepine receptor agonists, and melatonin receptor agonists.

Barbiturates and chloral hydrate were among the first agents used to induce sleep. These initial hypnotics targeted the GABA receptor. When benzodiazepines became available in 1980s, they were quickly accepted primarily because they were superior to the barbiturates in terms of safety. In the 1990s the benzodiazepine receptor agonists had demonstrated efficacy and were safer still so they quickly represented about 75% of a 43 million dollar market for hypnotics in 2005.[12] The newest agent ramelteon

became available in 2005 and targets the melatonin receptor. In addition to the approved hypnotics, many other substances are prescribed off-label for the treatment of insomnia.

Benzodiazepine receptor agonists

There are two classes in this category the classic benzodiazepines and the newer hypnotics collectively known as the Z drugs (zolpidem, zaleplon, zoplicone, and eszoplicone) that work on the alpha-1 subunit of the GABA-A receptor.

Five of the currently approved hypnotics fall within the benzodiazepine class, including triazolam, temazepam, estazolam, quazepam, and flurazepam (Table 15–1). The benzodiazepines are further classified as agents with short (<3 hours), medium (8–24 hours), and long (>24 hours) half-lives. The target is the benzodiazepine receptor site on the GABA-A receptor, a postsynaptic chloride channel that facilitates inhibition of the cortex. Due to their nonspecific binding nature, benzodiazepines possess other qualities including anticonvulsant properties, muscle relaxation, and memory impairment. Those prescribed for insomnia tend to have a rapid onset and short half-life so as to minimize adverse effects during the day; benzodiazepines with long half-lives are rarely used. Rebound insomnia can be a problem with prolonged use especially for shorter acting benzodiazepines.

Table 15–1 Hypnotics: Benzodiazepines

Drug	Dose Range	T_{max}	$t_{1/2}$	Metabolism/Excretion	Schedule	Pregnancy[110]	Main Side Effects
Estazolam (Prosom)	1–2 mg	0.5–6h	10–24 h	CYP3A and renal Fecal and renal	IV	X	
Flurazepam (Dalmane)	15–30 mg	0.5–1 h	2–3 h metabolites 50–150 h	Rapid with metabolites Renal	IV	X	Abnormal taste Blurred vision
Quazepam (Doral)	7.5–15 mg	2 h	39 h	Hepatic with metabolites Fecal and renal	IV	X	Indigestion
Temazepam (Restoril)	15–30 mg	1.2–1.6 h	3.5–18.4 h	First pass 8% conjugation Renal	IV	X	Hypotension Blurred vision
Triazolam (Halcion)	0.125–0.25 mg	2 h	1.5–5.5 h	Hepatic conjugated glucuronides Renal 80%	IV	X	Euphoria Rebound insomnia,
Clonazepam (Klonopin)	0.25–2 mg	1–4 h	30–40 h	Hepatic CYP3A Renal	IV	D	Excessive salivation, Glaucoma, Porphyria,

A number of meta-analyses of benzodiazepine use for the treatment of insomnia have been published.[13] Consistent findings across studies include polysomnographic evidence of improved sleep initiation (reduction of in the time it takes to fall asleep) and sleep maintenance (reduced arousals and awakenings improving the continuity of sleep). Benzodiazepines have also been shown to reduce SWS percentage and produce a prolongation in REM latency and reduction in REM percentage.[14]

Common side effects include dizziness, dyscoordination, and headache. As a rule, these agents produce more sedation and psychomotor slowing the following morning; hangover effect. In addition, benzodiazepines are associated with tolerance, dependency and withdrawal symptoms. Therefore, they are relatively contraindicated in patients with a history of substance abuse.[15] Some agents have active metabolites, which is of concern in patients with metabolic dysfunction and in the elderly, who are at increased risk of falls and orthostasis. There are additive effects when used in combination with alcohol or other CNS depressants. At higher doses, respiratory depression has been observed especially in those who have concurrent chronic pulmonary insufficiency or predisposed to respiratory regulation as in patients with sleep apnea.

This newer class of hypnotic differs from benzodiazepines in that they bind specifically to the alpha-1 subunit of the GABA-A receptor. This results in increased specificity for the sedative hypnotic effects without anxiolytic, myorelaxant and anticonvulsive properties.[16,17] Randomized controlled trials have demonstrated effectiveness for insomnia.[18] They decrease sleep latency, have variable effect of sleep maintenance and alterations of sleep architecture.[18] Direct comparison and meta-analysis studies have shown at least equivalence to benzodiazepines and to each other.[19] Therefore, the choice of agent depends on their specific pharmacokinetic profile matched to the clinical scenario, safety considerations and cost (Table 15–2).[20,21]

Table 15–2 Hypnotics: Benzodiazepine Receptor Agonists

Drug	Dose Range	T_{max}	$t_{1/2}$	Metabolism/Excretion	Schedule	Pregnancy[110]	Main Side Effects
Zolpidem (Ambien, Ambien CR)	5–10 mg; CR: 6.25, 12.5 MG	1.6 h	2.5–2.8 h	Hepatic CYP3A4, 2C9 Renal and fecal	IV	C	Depression
Zaleplon (Sonata)	5–20 mg	1 h	1 h	First Pass aldehyde oxidase Fecal and renal	IV	C	Abdominal pain, Severe renal impairment,
Eszopiclone (Lunesta)	1–3 mg	1 h	6 h	Hepatic with active metabolites Renal	IV	C	Bitter taste
Ramelteon (Rozerem)	8 mg	0.5–1.5 h	1–2.6 h	CYP1A2 Renal	NC	C	Reduce dose with concurrent use of fluvoxamine

The most common complaints seen include dizziness, headache, and nausea. Residual daytime somnolence was observed especially in the longer acting medications

although less commonly than with benzodiazepines. Although these agents have a lower risk of dependence, they can produce their own serious adverse effects. Concurrent use with alcohol or CNS depressants should be avoided. They should be used in caution with those who are at increased risk of respiratory depression such as in those who have sleep apnea. Although rebound insomnia was seen less frequently in clinical trials, abrupt withdrawal should be avoided. Recently, the FDA mandated that labeling include the risk of complex abnormal behaviors in sleep including sleep walking, sleep driving and sleep eating.

Zolpidem is an imidazopyridine derivative and has a rapid onset and short duration of action. These characteristics make this compound ideal for sleep onset insomnia. Randomized controlled trials have demonstrated reductions in objective parameters including sleep latency and number of nocturnal awakenings and an increase in sleep duration over a placebo-controlled group.[22,23] In addition other randomized controlled trials comparing zolpidem with approved benzodiazepines showed either comparable efficacy with improved daytime cognitive functioning in subjective responses and objective cognitive testing.[24,25] Its application in shift work sleep disorders is being explored.[26]

Zolpidem undergoes hepatic metabolism and, therefore, dose reduction is required in patients with hepatic insufficiency and the elderly. Some studies have suggested that zolpidem may be associated with rebound insomnia with prolonged use of 2–4 weeks and dependence in those with a prior history of substance abuse.[27] It is indicated for use for acute insomnia and use exceeding 7–10 days is not recommended, although postmarketing surveillance data in over 16,944 patients suggest longer term use it remains safe and effective.[28]

For those with sleep maintenance insomnia, the short duration of action may not be sufficient to maintain sleep for the course of the night. The continuous release preparation relies on two layers with different absorption properties and consequently increases the duration of action from 1.6 to over 3 hours. In contrast to zolpidem, there are no time restrictions in the packaging insert and the continuous release preparation is indicated for the treatment of sleep maintenance insomnia. Two double blind randomized parallel group clinical trials l eading to its approval demonstrated its safety and efficacy for up to three weeks.[29,30]

Zaleplon is a pyrazolopyrimidine. Several multicenter double-blind, randomized controlled parallel group trials have demonstrated that zaleplon safely decreases sleep latency with little residual effect in the morning.[31,32] Its shorter half life carries advantages of less residual memory and psychomotor untoward effects in contrast to zolpidem or triazolam.[33,34] Because of its pharmacokinetic profile, zaleplon may be taken at bedtime and again in the middle of the sleep period for individuals with sleep maintenance insomnia.

Once absorbed into the enterohepatic circulation, it undergoes extensive hepatic first pass metabolism by aldehyde oxidase, reducing its bioavailability to 30%. The remaining active drug, although primarily metabolized by CYP3A4, has several alternative metabolic pathways resulting in few drug interactions. A study of an elderly population demonstrated improved safety profile based on morning reaction times.[35]

Eszopiclone is a cyclopyrrolone, the S(+) enantiomer of zopiclone (which is not available in the United States). The exact binding site on the GABA-A receptor has not yet been determined.[36,37] Multicenter double blind placebo controlled parallel group studies have demonstrated reductions of sleep latencies in doses over 1mg, decreased wake after sleep onset, number of awakenings, and improved sleep efficiency.[38–40] It is the only agent that has been studied in a controlled fashion up to 6 months with demonstrated sustained effect.[40] The six month open labeled extension phase ofthis study also showed persistent effect without tolerance or withdrawal.[41] Its pharmacokinetic profile has established its niche as a good medication for sleep maintenance insomnia and it is the only agent FDA-approved for chronic insomnia.

One of the most commonly noted dose dependent side effects that resulted in discontinuation of use was its bitter taste. Since eszopiclone depends on the CYP3A4 enzyme system it is prone to numerous drug interactions. Dose reduction is recommended in patients with hepatic dysfunction and in the elderly.

Melatonin receptor agonists

Ramelteon is the only approved drug in this class. It has a high selectivity and potency for both the MT1 receptor in the SCN and the MT2 receptor with minimal affinity for the MT3 receptor, which has systemic effects.[42−44] Ramelteon has 15 times the affinity for MT1 than melatonin itself.

Double-blind randomized placebo controlled parallel group studies in primary insomnia subjects support its efficacy.[45,46] These studies demonstrate significant decrease in sleep l atency versus in the placebo group. In addition objective and subjective measures of total sleep time and wake after sleep onset also improved. Cognitive testing the day afterwards for digit symbol substitution and memory testing all were no different from placebo.

Although ramelteon is rapidly absorbed, absorption can be reduced by a high fat meal. It undergoes extensive first pass hepatic metabolism by its major hepatic isoenzyme CYP1A2 and thus is only 1.8% bioavailable. There is one active metabolite but its binding affinity is significantly less than ramelteon. Dose adjustment is required as in individuals also taking potent CYP1A2 enzyme inhibitors such as fluvoxamine, where maximum concentrations of ramelteon increase by up to 70-fold. Ramelteon is not recommended in patients with severe hepatic insufficiency.

Adverse effects include headache, dizziness, fatigue, and nausea. The safety profile in the elderly population appears to be favorable and only one dose, 8mg, is recommended for all ages. In addition, ramelteon exerts some untoward effects on the endocrine system, decreases testosterone levels and increases prolactin production, both of which may influence reproduction.

Ethanol

Easily accessible and relatively inexpensive, alcohol is the most common form of selfmedication for chronic insomnia.[47] Its hypnotic action may be related to nonspecific inhibition of the GABA-A receptor, although it also acts at other receptors such as the NMDA receptor, so there is a risk of tolerance, abuse and withdrawal seizures as well as having a variety of medical and social ramifications.

While many people perceive a positive effect on sleep latency, and many studies suggested decreases in sleep latencies based on subjective assessments but objective measures fail to demonstrate significant declines.[48] Polysomnographic studies suggest increased SWS sleep and decreased REM sleep in the first half of the night but since alcohol is metabolized rapidly in the gut and liver by alcohol dehydrogenase, by the second half of the night the subject withdraws from its effect; REM sleep rebounds causing vivid dreams and nightmares, and sleep is disrupted.[49] Furthermore, residual effects include decreased mean sleep latencies during a multiple sleep latency test and prolonged reaction times during cognitive tests the following day.[50]

Systemic effects including gastrointestinal discomfort need for urination and headache further disrupt sleep.[49] Alcohol can exacerbate both sleep apnea syndromes and RLS. Chronic use of alcohol can lead to insomnia.

Antihistamines

Diphenhydramine and doxylamine are approved as sleep aids and can be found in a number of over-the-counter preparations. Sedating antihistamines primarily exert their effect as H1 antagonists but they also have anticholinergic properties. The major advantages to these medications are accessibility without a prescription and cost.

The evidence supporting its use is limited. A small double blind placebo controlled trial involving 12 subjects compared temazepam 0.25 mg, diphenhydramine 50 mg and ethanol 0.6 g/kg to placebo. The decreased sleep latency and the residual daytime effects of temazepam and diphenhydramine were comparable.[50] A larger multicenter randomized placebo controlled parallel group 14 day study of diphenhydramine at a dose of 50 mg and a combination that included 187 mg of valerian and 41.9 mg of hops demonstrated that both were able to improve subjective measures of sleep latency and quality as assessed by sleep diaries but there were no demonstrable changes in the sleep architecture in comparison to placebo.[51] There was also no evidence for rebound over that 14 day period.

Common side effects include dizziness, somnolence, and dry mouth. Several of its adverse effects may be a result of its anticholinergic effects including urinary retention, glaucoma and gastrointestinal (GI) obstruction. Caution should be used in patients taking other CNS depressants, especially in an elderly population.

Sedative antidepressants

Sedating antidepressants are commonly prescribed for the treatment of insomnia. In general, these agents are significantly less costly than newer hypnotics and have a fairly low risk of abuse and tolerance. In addition, comorbid depression is observed in 3%[52] of people with chronic insomnia offering many insomniacs multiple benefits. Not only do these medications have anticholinergic properties they also have serotonergic properties.

However, this practice is based on limited data.[47,53–55] Beginning in the 1960s based on anecdotal evidence of the sedative side effect; amitriptyline was the first of these agents tried in this setting. There have been no studies demonstrating its efficacy in the setting of insomnia either with or without depression.

Trazodone, a tetracyclic antidepressant, is probably the most widely prescribed sedating antidepressant. Trazodone acts as a serotonin antagonist at low doses of 25–50 mg; doses exceeding 150 mg produce a serotonergic effect. Two small randomized clinical trials studied the efficacy of trazadone for insomnia.[56,57] Although trazodone at 50 mg was not as effective compared to zolpidem at 10 mg, it produced subjective improvement over placebo at two weeks and at doses lower than typically used for the treatment of depression.[56] The second study found that trazodone did not alter sleep latency or total sleep time but decreased wakefulness and stage 1 sleep and increased SWS percentage.[57] Patients should be warned of the risk of cardiac conduction abnormalities and priapism.

Mirtazipine, a newer and therefore less commonly prescribed agent which is gaining in popularity, is used for its sedative properties, but efficacy data are limited to patients with insomnia and comorbid depression. Adverse effects include weight gain, elevated cholesterol and triglyceride levels and residual daytime sleepiness.[47,53–55]

Neuroleptics

Neuroleptics with dopamine antagonists have long been associated with sedation. However, the older neuroleptics have adverse effects such as tardive dyskinesias and neuroleptic malignant syndrome that prohibit their use for insomnia. The newer atypical neuroleptics such as quetiapine and olanzapine hold more promise. In addition to being dopamine antagonists, they also have histaminergic and serotonergic properties.[47] Despite the lack of short term or long term efficacy data, patients report subjective improvement in sleep. Their use is limited in patients without other mental health disorders because they are prone to numerous drug interactions. Common limiting adverse effects include weight gain.

Herbals

Many insomniacs prefer over-the-counter herbal remedies to promote sleep, perceiving them as safe alternatives to costly prescription agents. Numerous herbals have been touted for the enhancement of sleep include hops, passion flower, lemon balm, skull cap, catnip, lavender, linden flower, and chamomile. None of these has sufficient data to evaluate their efficacy.[37]

The most commonly studied of these is melatonin. Despite a host of clinical trials, observations are limited due to the large number of available preparations. The soporific effects of exogenous melatonin differ from hypnotics. Instead it acts as an addition cue to initiate the cascade of pathways that signals the time for sleep. The timing of melatonin dose is the key to its efficacy. Optimally for sleep initiation, it should be administered during a period of time when endogenous levels are at their nadir as the pineal gland begins to release melatonin when natural light becomes dim. There have been studies to suggest that melatonin tends to be more efficacious in the elderly population with relatively low endogenous levels.[58] Melatonin has not produced demonstrable changes on PSG.[58]

In addition, melatonin has also been studied in the treatment of a number of circadian rhythm sleep disorders that result from shifts in the timing of the sleep period. In contrast to its use as a sleep aid, the timing of its administration depends on the goals for shifting the phase of sleep. For those who sleep late and wake late (delayed sleep phase syndrome), a study involving 60 patients demonstrated that 97% advanced their sleep time by 1.5 hours and their wake time by two hours when melatonin was given five hours prior to their desired bed time.[59] For those who sleep early and wake early (advanced sleep phase syndrome) melatonin should be administered in the early morning but the evidence for this is weaker because of side effects from the soporific effects of exogenous melatonin.

Exogenous melatonin exhibits relatively poor bioavailability and has the potential for producing a variety of systemic effects binding to the MT3, such as tachycardia, elevated prolactin levels, gynecomastia, hypothermia, and insulin resistance. Because melatonin can cause sleepiness, patients should use caution and should not operate heavy machinery after taking it. To date, the dose, timing, and long term consequences of melatonin are not known.[60]

Valerian root is used in many cultures to promote sleep. Valerian root is believed to have GABAergic properties and may increase SWS. Despite a number of randomized controlled studies investigating the use of valerian root in the treatment for insomnia, all the studies used subjective measures of sleep typically a visual analog scale and the results were mixed.[51] The dose ranges from 90–900 mg are difficult to control for and evaluate due to the variety of preparations.[61] This agent inhibits the CYP3A4 isoenzyme, which is prone to numerous drug interactions. When used in high doses of over 1000 mg withdrawal symptoms much like those seen with benzodiazepines have been reported.[61]

Kava is typically used in the South Pacific to promote relaxation and induce sleep. This agent was banned in Europe and Canada in 2001 due to associated fatal hepatotoxicity.[62] It remains available in the United States despite FDA warnings about the potential for serious adverse effects in 2002. It also inhibits a number of CYP isoenzymes and prone to a variety of drug interactions.[63]

Wake-Promoting Drugs

The ideal wake-promoting agent would produce a maximally alert state without adverse effects or negative impact on one's ability to sleep when desired.[64] There are a variety of available substances, although many are limited by tolerance and abuse potential. The FDA regulates many of these compounds strictly. The advent of modafinil in 1999 allowed broader applications because its improved safety and tolerance profiles (Table 15–3).

Table 15–3 Wake Promoting Agents

Drug	Dose Range	T_{max}	$t_{1/2}$	Metabolism/Excretion	Schedule	Pregnancy[110]	Main Side Effects
Amphetamine (Dexedrine, Desoxyn, Adderal, Adderal XR)	5–60 mg	1–2 h	20 h	Hepatic Renal	II	C	Glaucoma, Hyperthy roidism
Methylphenidate (Ritalin, Metadate, Methylin, Concerta)	10–60 mg	1–4 h	2.5–3.5 h	Renal	II	C	Glaucoma, Thrombo cytopenia
Modafinil (Provigil)	200–400 mg	2–4 h	40 h	Hepatic Renal	IV	C	Headache, Cardio vascular disease

Caffeine

Caffeine is the most commonly consumed drug in the world. Caffeine, a methylxanthine that blocks adenosine receptor, improves mental alertness and wakefulness. Typically it is ingested as coffee, teas, soft drinks, or chocolate confections. In addition, there are over-thecounter preparations. A typical 12-ounce brewed coffee contains 120–375 mg of caffeine.[65–67] Caffeine is absorbed within 15–120 minutes, hepatically metabolized and has a half life of 3.5–5 hours. Caffeine use may cause insomnia, particularly if ingested late in the day or in subjects with slow metabolism resulting in a prolonged effect. Adverse effects include restlessness, palpitations, hypertension, increased gastric secretion, urinary frequency, agitation, tremors and tachypnea.[8]

Amphetamines

Introduced in 1931, ephedrine was the first pharmacologic agents used to treat excessive daytime sleepiness (EDS). Since then, numerous formulations have become available, used predominately to improve mental alertness. Amphetamines, categorized as indirect-acting sympathomimetics, enhance monoaminergic release and block the reuptake of the monoamines in the synaptic cleft. It is the specificity to dopaminergic stimulation that may also be responsible for the wake-promoting effect.[8] The preparations available consist of racemic mixtures. The dextro-amphetamines have an increased affinity for dopamine and are more effective. The methylated form, known as methamphetamine, has increased CNS penetrance due to its lipophilic nature, which increases its efficacy.

Although its evidence for the treatment of excessive daytime sleepiness in narcolepsy is based on randomized, controlled trials, these studies are of limited value given they were performed prior to standardization of diagnostic criteria for narcolepsy, in small sample sizes and relied exclusively on subjective outcomes.[68–69] Dexedrine in 20 subjects with a history of sleepiness reduced subjective ratings of sleepiness.[70] Methamphetamines in 16 subjects with histories consistent for narcolepsy without cataplexy increased mean sleep latencies, reduced sleepiness and errors with driving simulators similar to the placebo control group.[71]

The common side effects include irritability, anxiety, insomnia, and weight loss. It should be used with caution in those with cardiovascular disease because it can cause tachycardia and hypertension. It should be avoided in those taking monoamine oxidase inhibitors. Psychosis has been observed at toxic doses. With prolonged use and/or high doses, tolerance can develop. Amphetamines are classified as Schedule II controlled substances due to their potential for abuse.

Methylphenydate

Introduced in 1956, methylphenidate has indications for the treatment of both attention deficit hyperactivity disorder and narcolepsy. Methylphenidate blocks the reuptake of monoamines, but does not appear to effect monoamine release. Therefore, it appears to have less abuse potential than amphetamines, and abuse in the narcoleptic population is not commonly seen.[72] It is the only medication hat has been studied in children from the age of 12 years on.[73]

Based on one randomized controlled trial and two case series in patients with narcolepsy, it appears to be effective in increasing wakefulness and better tolerated than amphetamines.[73–75] The randomized controlled study was designed as a series of trials involving a number of stimulants and methylphenidate reduced sleepiness based of maintenance of wakefulness tests.[74] These studies were limited by nonstandardized diagnostic criteria and the use of subjective outcomes.

It is a short-acting medication but there are longer acting preparations that allow single morning dosing and a more steady effect throughout the day. Much like amphetamines, common side effects are weight loss and restlessness. It should be avoided in those with cardiovascular disease and those taking monoamine oxidase inhibitors. It is contraindicated in patients who have glaucoma.

Pemoline

Pemoline, another indirect sympathomimetic, became available in 1975 and was an effective, although less potent, stimulant used for the treatment of narcolepsy. In June 1999, the FDA issued a black box warning for lethal heptotoxicity severe enough to require liver transplant and it was taken off the market in May 2005.

Modafinil

Modafinil has a novel and controversial mechanism of action. It does not rely on dopamine reuptake inhibition or monoamine release, but it may be related to the activation of the dopamine transporter (DAT) and enhances dopaminergic and aminergic transmission at the level of the anterior hypothalamus.[76–78] While modafinil was initially given the indication for the treatment of narcolepsy, subsequently it received indications for residual sleepiness associated with treated obstructive sleep apnea syndrome and to improve awake functioning for shift work sleep disorder because of its improved safety profile and tolerability. In contrast to amphetamines, modafinil does not appear to have addictive potential.[76]

The U.S. Modafinil in Narcolepsy Multicenter Study Group designed three large randomized, placebo-controlled trials comparing modafinil 200–400 mg and placebo in subjects with narcolepsy based on the 1997 International Sleep Disorders Classification criteria.[79–81] Compared with placebo, modafinil produced statistically significant improvements in objective measures based on mean sleep latencies based on both multiple sleep latency tests and maintenance of wakefulness and subjective tests of an Epworth sleepiness scale and quality of life measures (SF36).[81] Other multicenter placebo-controlled trials involving over 300 patients each all showed similar findings of improved objective and subjective measures of daytime sleepiness.[82–84]

Despite treatment with positive airway pressure treatment, some patients with obstructive sleep apnea (OSA) continue to have symptoms of excessive daytime sleepiness. Subsequent randomized controlled studies were performed comparing modafinil 200–400 mg with placebo as adjunctive treatment in subjects with residual daytime sleepiness and the results demonstrated durable improvements based on objective measures of mean sleep latencies found on multiple sleep latency tests and maintenance of wakefulness tests as well as subjective measures bases on Epworth sleepiness scale, Clinical Global Impression of Change and Functional Outcomes of Sleep Questionnaire.[85–87]

Based on several placebo-controlled trials in shift workers modafinil also has an indication for symptomatic treatment in waking function.[88–90] Studies demonstrated that subjects on placebo were twice as likely to make errors on performance vigilance testing as subjects randomized to modafinil 200 mg/day. Treatment was associated with fewer accidents or near accidents commuting home and statistically significant improvements in sleep latency based on multiple sleep latency tests.[88] A 12-week doubleblind controlled study showed that 200 mg of modafanil was superior to placebo in improving performance, and while it did not change the symptoms of sleepiness, the medication was efficacious and well tolerated during the 12-month open label extension phase.[89]

Modafinil may be administered once or twice daily. Adverse effects are often transient and include headache, nausea, nervousness and insomnia. Modafinil undergoes hepatic metabolism and specifically induces CYP3A4 and CYP2C19. As a result, the effectiveness of hormonal contraceptives may be reduced.[91]

Anticataplectic Medications

Cataplexy, a characteristic feature of narcolepsy, is the loss of distal skeletal muscle tone in response to a strong emotional stimulus and its intensity and frequency varies by individual. It represents an intrusion of REM atonia into wakefulness. This symptom tends to be an annoying and embarrassing. Tricyclic antidepressant medications have been first line treatment for cataplexy until recently when safer and more tolerable antidepressants have become available. Approved in 2002, sodium oxybate holds new promise for both the treatment of cataplexy and excessive daytime sleepiness in patients who have narcolepsy with cataplexy (Table 15–4).

Table 15–4 Anticataplectics

Drug	Dose Range	T_{max}	$t_{1/2}$	Metabolism/Excretion	Schedule	Pregnancy[110]	Main Side Effects
Sodium oxybate (Xyrem)	4.5 g–9 g	0.5–1 h	0.5–1h	Cytosolic Expired as CO_2 and H_2O	III	B	Hepatic dysfunction
Clomip ramine (Anafranil)	10–150 mg	2–6 h	19–37 h	Hepatic first pass Renal, fecal	NC	C	Acute myocardial infarction,
Protripty line (Vivactil)	5–60 mg	8–12 h	54–198 h	Hepatic Demethylation Renal	NC	Unknown	guanethidine or other peripherally-acting antihypertensives, cisapride,
Fluoxetine (Prozac)	20–60 mg	6–8 h	4–6 days	Hepatic Renal, fecal	NC	C	severe hepatic and renal dysfunction,

Tricyclic antidepressants (tca)

Based on years of clinical experience and committee consensus, stimulating TCAs have been used for the treatment of cataplexy.[69,92,93] Tricyclic antidepressants inhibit the reuptake of serotonin, norepinephrine, and dopamine in addition to having anticholinergic properties. Based on the canine model for narcolepsy, it is generally believed that the anticholinergic properties are responsible for the anticataplectic effect, although other agents without anticholinergic properties are also effective.[94]

Cloripramine is the only TCA to be studied for this purpose. One clinical series involving 16 subjects with the diagnosis of narcolepsy who were treated with clomipramine 25–125 mg and two control patients who were not treated demonstrated subjective improvement over controls in Epworth sleepiness scale and a cataplexy atonia rating scale.[95]

As a class, TCAs undergo hepatic metabolism, with some having active metabolites, and all are prone to drug interactions. Their use is limited by anticholinergic side effects including dry mouth, urinary retention, nausea, constipation, blurred vision, tachycardia, orthostatic hypotension, weight gain, and fatigue. Abrupt cessation may result in status catapleсticus or rebound cataplexy.

Selective serotonin reuptake inhibitors (ssris)

Selective serotonin reuptake inhibitors became available in the United States in 1987 with the introduction of fluoxetine. One study specifically examined zimelidine, an SSRI without anticholinergic properties, and found it to be an effective medication for cataplexy.[94] However, the exact mechanism for preventing cataplexy in humans is not clear.

Fluoxitine is the only SSRI studied in patients with narcolepsy with cataplexy who had failed a TCA. Fluoxitine 20 mg/day, reduced the number of self-reported cataplectic attacks in six subjects.[96] Fluoxitine tends to have more alerting properties, which is an advantageous characteristic in the treatment of narcolepsy with cataplexy, whereas paroxitine tends to have more sedating properties. Paroxetine and sertraline are used to treat cataplexy, but no efficacy data are reported. Anticataplectic doses of SSRIs tend to be comparably higher than effective TCA doses.

Common adverse effects include insomnia, tremor, anxiety, weight loss and sexual dysfunction. It should be avoided in those taking MAO-I or other serotonergic drugs.

Sodium oxybate

Its reputation as the so-called date rape drug delayed it approval in the clinical realm. However, due to its efficacy the FDA approved it for the treatment of cataplexy in 2002 and later for excessive daytime sleepiness in the setting of narcolepsy. Sodium oxybate is gamma hydroxybuterate (GHB) an endogenous byproduct of GABA and may act independently on its own receptors.[97,98] At pharmacological concentrations, it increases dopamine levels and serotonin turnover, and stimulates growth hormone release by interacting with GABA-B receptors.

Although this agent was initially available in 1960, small case series[99,100] suggesting its efficacy in narcolepsy were not published until the 1980s. Based on this and other smaller randomized controlled studies, the U.S. Xyrem Multicenter Study Group designed four large multicenter randomized controlled trials in the 1990s to investigate the safety and efficacy of sodium oxybate in the treatment of narcolepsy with cataplexy.[101–104] Initial studies focused on the decreased number of cataplectic attacks in a dose dependant manner as recorded by patient diaries at the 6g and 9g doses. These results were demonstrated to be durable over the course of 12 months based on an open label extension phase and there was no evidence of rebound cataplexy on acute withdrawal. Since there were significant improvements in secondary outcomes of daytime sleepiness as measured by Epworth sleepiness scale and maintenance of wakefulness test, further studies investigated overnight polysomnographic data that suggests statistically significant increases in the percentage of slow wave sleep and stabilization of REM periods.

After rapid absorption there is an extensive first pass effect and then the drug is converted by GHB dehydrogenase to succinic semialdehyde where it enters the Krebs cycle to be expired as carbon dioxide and water. Sodium oxybate is a schedule III controlled substance and is administered through a single central pharmacy in the United States. The recommended dosage is 4.5–9g/day given in two doses: at bedtime and 2.5–4 hours later. The first dose should be taken once the patient is prepared for and sitting in bed, due to its rapid absorption. High fat meals can reduce absorption by as much as 50%. There is minimal residual effect in the morning because it has such a short half life.

Common side effects include headache, nausea, dizziness, pain, and enuresis. Toxic effects in an overdose situation include tremor and seizures. This medication is contraindicated in patients with semialdehyde dehydrogenase deficiency, a rare autosomal recessive disorder characterized by hypotonia, ataxia and developmental delay. Due to its high sodium content, it should be used with caution in patients with cardiac or renal dysfunction. Concomitant use with alcohol or other CNS depressants can exacerbate sleep apnea syndromes.

Drugs to Treat Sleep-Related Movements

Restless legs syndrome, the prototypical sleeprelated movement disorders, is the only disorder with approved pharmacological treatment. Although first described by Willis in 1672,[105] it was not until Ekbom[106] in 1945 defined the clinical features that treatments were investigated. Periodic limb movements of sleep (PLMS) as measured by actigraphy or PSG are associated with 80%–90% of patients with RLS and are often used as surrogate markers of efficacy of treatment.[52] Initially effectively treated with opioids, the pathophysiology of RLS is now known to involve the cerebral iron-dependent dopminergic systems leading to a variety of treatment options (Table 15–5).[107–110]

Table 15–5 Medications Used for the Treatment of RLS

DOPAMINE AGONISTS

Drug	Dose Range	T_{max}	$T_{1/2}$	Metabolism/Excretion	Pregnancy[110]	Main Side Effects
Levadopa/Carbidopa (Sinemet)	50–200 mg	0.5–2 h	0.75–1.5 h	Hepatic Renal, fecal	Unknown	melanoma, glaucoma, hepatic and renal dysfunction, diabetes mellitus, risk of gastrointestinal bleeding, phenylketonuric,
Ropinerole (Requip)	0.25–3.0 mg	1–2 h	6 h	Hepatic CYP1A2 Renal	C	severe hepatic or renal dysfunction Ciprofoxicin
Pramipexole (Mirapex)	0.125–1.5 mg	2 h	8 h	— Renal	C	hallucinations renal dysfunction

OPIODS

Drug	Dose Range	T_{max}	$t_{1/2}$	Metabolism/Excretion	Schedule	Pregnancy[110]	Main Side Effects
Tramadol (Ultrani)	50–300 mg	1.5–2 h	6 h	CYP2D6, 3A4 Renal	NC	C	increased seizure risk
Codeine	30–180 mg	1–2 h	2.5–3.5 h	Glucuronidation CYP2D6 Renal	II	C	hypothyroidism, seizures
Hydrocodone	5–30 mg	1.3 h	3.8 h	Déméthylation Renal	II	Cannot rule out	puritis, urinary retention
Propoxyphene	100–600 mg	2–2.5 h	6–12 h	Hepatic —	IV	Unknown	
Oxycodone	5–30 mg	1.3 h	3.5–4 h	First pass CYP2D6 Renal	III	B	Convulsive disorders
Methadone	2.5–20 mg	1–7.5 h	7–59 h	CYP3A4, 2B6, 2C19,2C9, 2D6 Fecal, renal	II	C	QT interval prolongation and Torsades de pointes

ANTICONVULSANTS

Drug	Dose Range	T_{max}	$t_{1/2}$	Metabolism/Excretion	Pregnancy[110]	Main Side Effects
Gabapentin (Neurontin)	300–3600 mg	1.5–4 h	5–7 h	— Renal	C	Renal dysfunction, peripheral edema avoid abrupt discontinuation
Carbamazepine (Tegretol, Carbatrol)	200–600 mg	4—5 h	12–17 h	CY3A4 Renal, fecal	C	Bone marrow suppression, hepatitis, Rash, photosensitivity,
Valproic Acid (Depakote)	300–600 mg	4–8 h	9–16 h	Hepatic Renal	D	Hepatotoxicity hyperammonemia, pancreatitis, thrombocytopenia, inhibit lamotrogine metabolism Weight gain, alopecia, tremor

Iron

Patients with RLS should be routinely screened for iron deficiency as this is the most frequent secondary cause of RLS. Serum ferritin or iron saturation studies, measures of iron stores, are recommended since serum iron levels and total iron binding capacity lack sensitivity in detecting this disorder. Iron replacement is recommended for those with ferritin levels less than 50 μg/L or iron saturations less than 16%.[109]

Ferrous sulfate 325mg administered one to three times a day is recommended. Vitamin C, which acidifies the stomach, should be administered simultaneously to optimize gastric absorption.[109] Treatment should continue until serum ferritin exceeds 50 μg/L and/or iron saturation exceeds 20% and efficacy of treatment should be evaluated at three months. Constipation is common and may require treatment by increasing dietary fiber content or the use of a stool softener.

Levodopa

Levodopa has been a primary treatment of RLS for nearly 20 years.[111] Levodopa is converted to dopamine in the CNS. Carbidopa is administered simultaneously to minimize peripheral conversion. Both rapid release and sustained release L-dopa have been studied.[112–115]

Based on nearly 24 trials, including over 10 randomized controlled trials, levodopa effectively reduces the severity of RLS.[111] Compared to placebo, levodopa significantly reduces PLMS based on actigraphy in the first half of the night and improved subjective sleep and improved daytime functioning on a variety of subjective questionnaires.[113] While bioavailability is reduced with the controlled release formulation, it is superior in many cases in preventing rebound or recurrent RLS symptomology in the latter half of the sleep period as the medication wears off. Therefore, the combination of the two has been suggested to improve control.

This is the only drug so far that has evaluated children with RLS ages 4–18 with a history of ADHD who failed stimulants. This open label study involving eight children showed decreased limb movements and improved symptoms with regards to both RLS and ADHD symptoms.[116]

However, one of the most important side effects of levodopa is the phenomenon of augmentation.[117] Augmentation is defined as progressive advancement of RLS symptoms to earlier in the day, extension of symptoms to other body parts including the arms and the trunk, and despite increases in medication dose its effectiveness and duration decrease. Augmentation is observed in up to 82% of patients with RLS taking levodopa.[111] Maintaining the lowest effective dose may prevent the development of augmentation; drug discontinuation is required in some cases.

Levodopa's short half life makes it an ideal agent for people with intermittent RLS. Adverse effects included dry mouth and nausea and glaucoma. Dystonia is not seen in patients with RLS as is seen in patients being treated for Parkinson's disease.

Dopamine agonists

As augmentation became a recognized limitation of levodopa therapy, dopamine agonists were studied as an alternative. The dopamine agonists fall into two categories: ergotderived and nonergotamine dopamine agonists. The three most studied dopamine agents (pergolide, ropinirole, and pramipexole) are effective and have less incidence of augmentation. In addition, sleep attacks and dystonia that are described in patients with Parkinson's disease are not seen in as frequently in this population. Common adverse effects include headache, nausea, orthostatic hypotension, and insomnia.

Pergolide, an ergot-derived dopamine agonist and one of the most studied in the use of RLS, acts on the presynaptic D1 and postsynaptic D1 and D2 receptors. However, ergotderived medications are associated with fibrosis of the cardiac valves, pericardium and pleural tissues, which had limited its use. In March 2006, pergolide was taken off the market in the United States.

Several double-blind randomized cross over placebo controlled studies demonstrated improvement in subjective symptoms of RLS, especially in those who previously failed levodopa, decreased PLMS, with and without arousals as measured by polysomnography and improved objective measures of total sleep time, time in bed, and sleep efficiency.[118,119,111]

The longer duration of action provided symptomatic coverage throughout the night. The frequency of augmentation is substantially less with the dopamine agonists in general and is estimated to be 15% with pergolide.[118]

In May 2005, ropinirole became the first agent ever approved for the treatment of RLS. In contrast to pergolide, ropinirole is a nonergot dopamine agonist that binds to the D3 receptor more than the D2 or D4 receptors.

Randomized controlled trials using standardized diagnostic criteria and two smaller studies[120–124] demonstrated subjective symptom improvement of daytime sleepiness, sleep disturbance, adequacy, and quantity by day one of therapy and good tolerance. Ropinirole significantly reduced the number of PLMS based on objective PSG measures. Other PSG changes include decreased sleep latency and increased stage 2 sleep compared to placebo, suggestive of increased stability of sleep.

Ropinirole should be titrated starting at a dose of 0.25 mg and increasing weekly to symptomatic relief at 1.5–6 mg/day. The slow titration schedule may not offer immediate relief. Ropinirole levels may rise with common medications such as ciprofloxacin. Augmentation is observed in 20%–30% of patients (REF).[125]

Pramipexole is the second agent approved by the FDA in November 2006 for the treatment of RLS. Like ropinirole, pramipexole is a nonergot dopamine agonist that is preferentially a D3 agonist over the D2 or D4 receptors.

The indication was based on several small open-label and two, more recent, large multicenter randomized controlled trials that demonstrated significant improvement in subjective symptoms and quality of life measures within the first week and at the initial dose of 0.125 mg.[126–129] Studies show significant reduction of PLMS. Secondary efficacy measures based on PSG alterations in nine patients show significantly increased REM latency and decreased total REM sleep time.[126] Based on a retrospective review, about a third of patients experienced augmentation within the first 2.5 years of treatment, but symptoms resolved with reduction of dose.[127]

Opioids

While opioids were the first treatment for RLS and remain among the most effective, their use is restricted in general to more refractory cases due to concerns of tolerance and addiction. Although the mechanism of action is not clearly related to the pathophysiology of RLS, opioids provide symptomatic relief of RLS and increase the arousal threshold.

Oxycodone and propoxyphene have been demonstrated in randomized trials. A multicenter retrospective study found that 23% of RLS patients had been on an opioid at some point in their treatment and sustained benefit was realized in those treated over six years.[130]

Common adverse effects include nausea, vomiting, constipation, lightheadedness, and sedation. Opioids should be used with caution in patients concurrently taking other CNS depressants as it may exacerbate sleep apnea due to the potential for respiratory depression. The dose should be decreased in elderly patients and those with respiratory, hepatic, or renal dysfunction. The longer-acting agents such as methadone, a synthetic opioid that works on the μ receptor, may have less addictive and tolerance potential.

Anticonvulsant medications

Anticonvulsant medications have long been recognized as effective treatments in a variety of pain disorders and are currently first-line therapy for painful RLS. The mechanisms by which they convey pain relief is not clearly understood but presumably involve central pain pathways.

Carbamezepine was one of the first of this class to be tried in the treatment of RLS. Based on two small controlled studies using doses under 600 mg/day there appeared to be benefit over placebo.[131] Newer anticonvulsants with better side effect profiles and less drug interactions have become available. Controlled studies of gabapentin show consistent improvement in RLS symptomatology on subjective rating scales, decreased PLMS, and improvement in sleep architecture (total sleep time, sleep efficiency, slow wave sleep and decreased stage 1 sleep).[132] At higher doses, sedation and dizziness may limit use. One study that compared slow release valproic acid 300–600 mg to

rapid release levodopa 100–200 mg demonstrated comparable efficacy for subjective and polysomnographic measures.[133]

Hypnotics

Benzodiazepines have long been used for the symptomatic relief of RLS, although largely based on anectodotal observation. A few small open-label and randomized controlled studies show benzodiazepines improved RLS symptoms despite unchanged PLMS frequency on PSG. It is believed that consolidated sleep improves daytime function.[134] Clonazepam is preferred because of its long half life. Studies of nonbenzodiazepine hypnotics for RLS are lacking.

Clonidine

Clonidine is an α2 blocking agent that is believed to exert sedative properties by activation of the locus ceruleus. Small randomized controlled studies demonstrate that clonidine improves subjective symptoms, but does not appear to reduce PLMS during PSG.[135] The recommended starting dose is 0.1 mg in the evening, increased every few days to effect or a maximal dose of 1 mg. Adverse effects included dry mouth, decreased cognitive functioning, lightheadedness, sedation, constipation and reduced libido. As an antihypertensive, hypotension can be a limiting factor and abrupt discontinuation can result in profound rebound hypertension and tachycardia.

Specific sleep disorders

Released in 2005, the International Classification of Sleep Disorders second edition (ICSD2) details over 80 sleep disorders falling largely under six primary categories.[52] Over the last decade, these categories have expanded markedly based on improved understanding of the pathophysiology, polysomnographic manifestations and effective therapies. Treatment approaches for these primary classes of disorders are addressed here (Table 15–6).

Table 15–6 Classification of Sleep Disorders
ICSD-2 Sleep Disorder Major Treatable Categories
1. Insomnias
2. Sleep-Related Breathing Disorders
3. Hypersomnias Not Due to a Sleep-Related Breathing Disorder
4. Circadian Rhythm Sleep Disorders
5. Parasomnias
6. Sleep-Related Movement Disorders

Insomnia

Insomnia is defined as difficulty initiating sleep, maintaining sleep, early morning awakenings, or chronically nonrestorative or poor quality sleep despite adequate opportunity and circumstance for sleep leading to daytime impairment.[52] Daytime impairment includes fatigue or daytime sleepiness, attention, concentration or memory impairment, poor social, occupational or academic performance, mood disturbance or irritability, motivation, energy or initiative reduction, proneness for errors/ accidents at work or while driving, tension, headaches, or GI distress due to sleep loss or worries about sleep.[52]

Insomnia affects 60 million people in the United States and is more common in women, the elderly and people with psychiatric illness. The National Sleep Foundation 2005 Sleep in America Poll found that 54% of adult Americans experienced symptoms of insomnia a few nights a week.[136] The survey reported that 29% of respondents sought medical advice for insomnia and 14% self-medicated with alcohol, over-the-counter preparations or herbal supplements. Insomnia is classified as primary or secondary; secondary cases are those associated with medical and psychiatric disorders and drug or substance use. Treatment of secondary insomnia includes optimizing the management of the causative condition. Insomnia is also classified as acute (<3 months) or chronic insomnia (>3 months). Acute (adjustment) insomnia is frequently related to a stressful event such as death of a loved one or other traumatic life events. Chronic (psychophysiological) insomnia results from established maladaptive sleep behaviors (Table 15–7).

Table 15–7 Subclassification of Insomnia
Adjustment Sleep Disorder (Acute Insomnia)
Psychophysiological Insomnia
Paradoxical Insomnia (formerly Sleep State Misperception)
Idiopathic Insomnia
Insomnia due to mental disorder
Inadequate Sleep Hygiene
Behavioral Insomnia of Childhood
Sleep-onset Association Type
Limit-setting Sleep Type
Combined Type
Unspecified Type
Insomnia due to a medical condition
Insomnia due to a drug or substance
Insomnia not due to a substance or known physiological condition, unspecified (Nonorganic Insomnia, NOS)
Physiological (organic) insomnia, unspecified; (Organic Insomnia, NOS)

Pathophysiology

Although a single specific mechanism for insomnia is not known, the end organ is the cerebral cortex. Proposed theories include over-active waking mechanisms resulting in a hyperarousal state and insufficient sleep maintenance systems.[53] The primary goal of treatment is to promote cortical inhibition and reduce environmental triggers.

Targets

Almost all of the neurotransmitter systems involved in the regulation of sleep and wake have been a target. The major inhibitory system, the GABAergic system has been the main target. Barbiturates, benzodiazepine, and benzodiazepine receptor agonists all target the postsynaptic GABA-A receptor complex, specifically the alpha-1 subunit of the benzodiazepine site, which conveys more of the sedative effect. The newest hypnotic targets the melatonin receptor within the suprachiasmatic nucleus that regulates sleep-wake cycle. The histaminergic system promotes wakefulness through the tubomammilary nucleus in the posterior hypothalamus; nonspecific blockade of the H1 receptor produces sedation. Over-the-counter antihistamines, such as diphenhydramine, act on the H1 receptor and have anticholinergic properties. Sedative antidepressants exert

their inhibitory effects on numerous neurotransmitter systems including the cholinergic, noradrenergic and serotonergic sites; all of which have arousing properties. The dopaminergic system is the primary target for the neuroleptics used in insomnia.

Management

Despite the prevalence of insomnia, healthcare providers seldom screen their patients for this and other sleep disorders. A thorough sleep history can identify precipitating and perpetuating causes and temporal characteristics such as sleep onset, sleep maintenance or early morning awakenings. Polysomnography is typically not required unless there is a suspicion of sleep apnea or periodic limb movement disorder (PLMD), and perhaps in refractory cases.[137] The majority of acute insomnia resolves spontaneously.

Individuals with chronic insomnia require treatment typically with behavioral and/or pharmacological therapy. Cognitive behavioral therapy (CBT) encompasses a variety of strategies aimed at correcting maladaptive sleep behaviors and perceptions and typically performed under the instruction of a sleep medicine expert. Critical to the treatment is to practice good sleep hygiene (Table 15–7). Several large meta-analyses have evaluated treatment modalities.[138–140] There is benefit in the short term pharmacotherapy but the long term consequences are lacking. Behavioral therapy demonstrated sustained benefit from six months to two years without side effects. Comparing pharmacotherapy to behavioral therapy, there may be a greater reduction in sleep latency with behavioral therapy than medications alon.[140] The American Academy of Sleep Medicine and other authorities recommend CBT in patients with chronic insomnia, including the elderly and those who have a contraindication to pharmacotherapy (Tables 15–8 and 15–9).[141,142]

Table 15–8 Sleep Hygiene

1. Avoid napping during the day.
2. Avoid stimulants such as caffeine, nicotine, and alcohol too close to bedtime.
3. Vigorous exercise in the morning or late afternoon or relaxing exercise like yoga in the evening can promote good sleep.
4. Avoid large meals close to bedtime.
5. Ensure natural light exposure to entrain the circadian rhythm.
6. Maintain regular and relaxing routines at bedtime.
7. Associate the bed with sleep and restrict other activities from the bed such as watching TV, listening to the radio or reading.
8. Maintain a comfortable sleep environment.

Table 15–9 Algorithm for the Treatment of Insomnia
Acute insomnia: short term medications Sleep onset: fast onset and short duration Sleep maintenance: longer half life Early morning awakening: either a longer half life or a very short acting
Chronic insomnia Evaluate for a comorbid sleep disorder Cognitive behavioral therapy Pharmacotherapy: fixed intermittent dosing
Revaluate to see if medications can be tapered

The choice of hypnotics depends on the type of symptoms the patient has and the pharmacokinetic profile of the hypnotic. The goal is to match the symptom with the complaint. Those with difficulties initiating sleep should take quick onset short acting medications and those with sleep maintenance insomnia should take longer acting medications. Although the newer hypnotics have a better side effect profile, for many patients, benzodiazepines remain much more cost-effective.

Future targets

The future of pharmacological insomnia therapy will be to develop more effective agents with improved safety profile, tolerability, and affordability with little or no abuse potential. Targets under active investigation include selective extrasynaptic GABA-A receptors (SEGA) that are diffusely distributed in the CNS, but particularly in the cortex, thalamus and the limbic system and may influence chloride conductance independent of GABA.[47] Melatonin agonists should be further explored. Novel approaches include manipulating the serotonergic system, and blocking central histamine and orexin systems.[47]

Sleep-Related Breathing Disorders

Sleep-related breathing disorders are a heterogeneous group of conditions with diverse pathophysiology that share findings of disordered respiration during sleep (Table 15–10). Respiratory events are differentiated into apneas and hypopnea and the types are classified as obstructive or central (Figure **15–4**). Obstructive hypopneas or apneas are characterized by a transient reduction in or complete cessation of breathing lasting longer than 10 seconds respectively.[143] A respiratory effort related arousal (RERA) is characterized by a sequence of breaths associated with increasing respiratory effort that can be measured by esophageal manometery leading to an arousal from sleep lasting longer than 10 seconds.[143] In contrast, central apneas are characterized absent airflow breathing and respiratory effort lasting longer than 10 seconds. Frequently, at the termination of a respiratory event, a cortical arousal occurs and disrupts sleep continuity. Respiratory events can also result in a fall in O2 saturation and a rise in arterial pressure of CO2 ($PaCO_2$). The severity of the disorder can be measured as the total number of apneas and hypopneas per sleep hour: an apnea hypopnea index (AHI). Alternatively, some sleep laboratories express the severity as a respiratory disturbance index (RDI), which is less strictly defined and in some labs may be equivalent to an AHI but in other labs may include RERAs. The operational definition specifically for obstructive sleep apnea syndromes used for research purposes stratifies the severity of the AHI as mild (5–15 events per hour), moderate (15–30 events per hour), and severe (greater than 30 events per hour).[143]

Table 15–10 Subclassifcation of Sleep-Related Breathing Disorders
Central Sleep Apnea Syndromes
Primary Central Sleep Apnea
Other Central Sleep Apnea due to a medical condition
Cheyne Stokes (C-S) Breathing Pattern
High Altitude Periodic Breathing
Central Sleep Apnea due to a medical condition, not C-S or High Altitude
Central Sleep Apnea due to a drug or substance
Other Sleep-Related Breathing Disorder due to a drug or substance
Primary Sleep Apnea of Infancy (formerly Primary Sleep Apnea of Newborn)
Obstructive Sleep Apnea Syndromes
Obstructive Sleep Apnea, Adult
Obstructive Sleep Apnea, Pediatric
Sleep-Related Hypoventilation/Hypoxemic Syndromes
Sleep-Related Non-obstructive Alveolar Hypoventilation, Idiopathic
Congenital Central Alveolar Hypoventilation Syndrome
Sleep-Related Hypoventilation/Hypoxemia due to a medical condition
Sleep-Related Hypoventilation/Hypoxemia due to pulmonary parenchymal or vascular pathology
Sleep-Related Hypoventilation/Hypoxemia due to lower airways obstruction
Sleep-Related Hypoventilation/Hypoxemia due to neuromuscular or chest wall disorders
Other Sleep-Related Breathing Disorder
Sleep Apnea/Sleep-Related Breathing Disorder, unspecified (Sleep-Related Breathing Disorder, NOS)





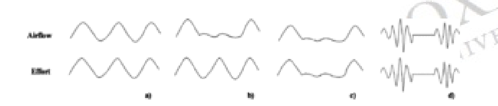


Figure 15–4.
Respiratory effort. Types of respiratory effort: (a) Normal breathing; (b) Obstructive event with no airflow and retained effort; (c) Central event with no airflow or effort; (d) Cheyne Stokes Respiration with crescendo decrescendo respiration separated by a central apnea

Anatomy

Automatic respiratory control occurs within the brainstem. The dorsal respiratory group that resides in the ventrolateral aspect of the nucleus tractus solitarius receives afferent projections via the glossopharyngeal nerve and the vagus nerve from the chemoreceptors that are sensitive to hypoxia and hypercapnea in the carotid bodies and the baroreceptors sensitive to hypoxia in the lung.[144] The respiratory pacemaker resides within the ventral respiratory group, which projects to the phrenic nerve and the spinal nerves that innervate the diaphragm and the intercostals muscles and to the hypoglossal and recurrent laryngeal nerve that innervate the muscles of the upper airway. The pontine respiratory group further modulates inspiratory and expiratory patterns. The forebrain makes adjustments to allow for other pharyngeal functions such as speaking and swallowing. During wakefulness cortical control can further stimulate respiratory patterns. All these structures work in conjunction to regulate the respiratory rate and rhythm.

Pathophysiology

Several factors contribute to apnea during sleep. Wakefulness is its own ventilatory stimulus for respiration, the loss of which results in the reliance on automatic regulation of ventilation alone. In addition, the reduction or loss of upper airway tone during sleep, especially during REM, increases the likelihood of occlusion of the upper airway. Furthermore, the recumbent position decreases radial traction on the upper airway further promoting collapse. Under normal conditions as elevations in $PaCO_2$ rises stimulates ventilation. When the $PaCO_2$ falls below a critical level, this results in a central apnea: the apnea threshold. During sleep there is a decreased chemosensitivity and blunted response to $PaCO_2$, which rises about 4–6 mm/Hg above that of the waking state.

Obstructive sleep apnea syndrome (OSAS) is the most common sleep related breathing disorder. It is characterized by recurrent full or partial occlusion of the upper airway during sleep. As a result of these occlusions, oxygen saturations fall and repetitive arousals at the termination of each event results in sleep fragmentation and daytime fatigue. The Wisconsin Cohort study estimated the prevalence as 2% in women and 4% in men between the ages of 30–60.[145] They further determined that the majority of these people are not clinically diagnosed. The prevalence increases with age and postmenopausal women approach the rate of men. Obesity and male gender are major risk factors for OSAS.

In its clinical presentation, patients with OSAS will complain of daytime sleepiness or difficulty initiating sleep while their bed partners typically report snoring and witness apneic events. Other clinically associated features include morning headache, dry mouth, heartburn, nocturia, diaphoresis and impotence. Frequent clinical findings include a BMI greater than 28 kg/m^2, neck circumference over 40 cm and narrowing of the pharyngeal space. The diagnosis is made by overnight polysomnography with an AHI of greater than five events per hour in the presence of symptoms clinical symptoms. Comorbid conditions that are risk factors for OSAS include obesity, hypertension, cardiovascular disease, and cerebrovascular disease. If OSAS is left untreated, it can exacerbate these conditions.

Rationale for treatment

The goal for treatment in OSAS is to avoid or overcome the upper airway obstruction. Weight reduction can be effective in increasing airway luminal diameter. Nasal corticosteroids or short acting decongestants can minimize nasal congestion and thereby reduce nasal airflow resistance. Avoiding CNS depressants such as alcohol that diminish central responses to hypoxia and hypercapnea can also be effective therapy. Altering the patient's sleep position (supine position can exacerbate OSAS) is an alternative option. Mechanical treatments such as surgical procedures or dental devices are options but positive pressure ventilation is the most effective.

Positive pressure ventilation became available in 1981 and the American Academy of Sleep Medicine (AASM) practice parameters published in 2006 suggested that it is safe and effective and should be the standard of treatment for OSAS.[146] The administration of pressurized air through a nasal mask provides a pneumatic splint that maintains airway patency allowing for normal respiration without disruption to sleep, no matter where the level of obstruction occurs. The pressurized air can be delivered in a continuous fashion (CPAP) or in a bilevel fashion. However, many patients are unable to tolerate and/or adhere to this treatment. They complain of the noise of the machine, discomfort from the mask interface, nasal and pharyngeal discomfort, claustrophobia and ineffectiveness at resolving the symptoms. Working with their provider can improve tolerability.

Surgical procedures are an option for those who have an upper airway obstruction that can be surgically approached. Tracheostomy was the first surgery done for OSAS because it bypassed the upper airway obstruction. Because of substantial morbidity from the procedure and the advent of less invasive procedures (i.e., rhinoplasty, uvuloplasty, or tonsillectomy), tracheostomy is less frequently performed for this indication. Uvulopalatopharyngoplasty (UPPP) initially used for snoring was found to be 43%–

67% effective for OSAS also.[147] Dental devices open the upper airway by pulling the soft tissue forward by using the teeth to gently advance the mandible.[148] However, those who are prone to temporomandibular joint symptoms do not tolerate this treatment well and dental positioning is insufficient therapy for more severe cases of OSAS.

Guidelines published in 2006 by AASM evaluate current recommendations for medical therapies in the treatment of OSA.[149] The only FDA approved medication for the use in patients who have obstructive sleep apnea and who are compliant with positive pressure ventilation, but still experience daytime fatigue is modafanil. Modafanil should only be used adjunctively; it represents symptomatic treatment for daytime sleepiness, and does not prevent potential cardiovascular consequences resulting from recurrent episodic nocturnal airway occlusion.

Antidepressants such as protriptyline, fluoxetine, and buspirone can stimulate both central pathways and peripheral nerves to the oropharynx.[150,151] The anticholinergic properties can increase neuronal activity in the hypoglossal nerve and in the recurrent laryngeal nerve and thus increase upper airway tone. Many antidepressants are REM suppressants and by decreasing the time in REM sleep, incidentally decrease the impact of REM atonia. The use of oxygen, although tempting in sleep apnea syndromes associated with severe desaturations, should be considered with caution in those patients who are hypercapnic and have respiratory acidosis, because the oxygen can prolong the apneic period. Although there may be some situational benefits, there is insufficient evidence for the AASM to recommend the use of these treatments.

Central sleep apnea syndromes (CSAS) are characterized by a lack of ventilatory effort during sleep. The lack of effort can be related to two separate factors. Mechanical abnormalities of the respiratory musculature result in alveolar hypoventilation and hypercapnea and are associated abnormalities of ventilation, which occur while awake as well as asleep. A number of neuromuscular disorders including myasthenia gravis, amyotrophic lateral sclerosis, postpolio syndrome and myopathies such as acid maltase deficiency are associated with CSAS. In contrast, conditions associated with increased chemosensitivity for the signaling of ventilation during sleep with normocapnea or hypocapnea and altered apnea thresholds lead to unstable respiratory patterns. Cheynes Stokes respiration, an example of this type of breathing pattern, is characterized by an oscillating pattern of crescendo decrescendo breathing separated by a central apnea or hypopnea. It occurs more frequently as patients get older and is associated with congestive heart failure and cerebrovascular disease.

Targets

The goal of treatment is to stabilize the ventilatory drive but there are no FDA approved treatments. Positive pressure ventilation is frequently used to open the upper airway during central respiratory events and minimize ventilatory overshoot, which leads to ventilatory stability in nonhypercapneic apnea. Bilevel positive pressure is typically used for those with impaired motor control of the respiratory muscles. Although a number of respiratory stimulants have been tried, the results have not been encouraging. Pregnant women and women during the luteal phase of their menstrual cycle have increased ventilatory drives when progesterone levels are high.[152] Progesterone may increase upper airway tone and alter sensitivity to CO_2 thus increasing ventilatory drive.[153,154] However, there are no controlled studies that demonstrate the efficacy of treatment with exogenous progesterone in the management of CSAS. Theophylline increases the tone in the upper airway and enhances the contractility of the diaphragm, but limited studies have not shown symptomatic benefit. Furthermore, theophylline has a narrow therapeutic window and is therefore difficult to achieve therapeutic serum levels in the absence of side effects.[155] Acetazolamide, a carbonic anhydrase inhibitor, may cause a metabolic acidosis thus stimulating respiration, but again the studies are not promising.[156] Oxygen in nonhypercapneic central apnea stabilized ventilatory overshoot based on limited short term data. Carbon dioxide has been effective by elevating the $PaCO_2$ above the apnea threshold and reducing the number of apneic events.[157]

Future targets

Sleep apnea syndromes are multifactorial in etiology and therefore a multidisciplinary approach may improve management. There have been no randomized studies that clarify which patients respond best to weight reduction and the best medical therapies to achieve this goal. Other wake promoting stimulants or respiratory stimulants may also prove to be of benefit in medically refractory sleep apnea. Serotonergic agents are appealing targets as they can act both centrally at the brainstem and peripherally at the nerves innervating the oropharynx.

Hypersomnia Syndromes

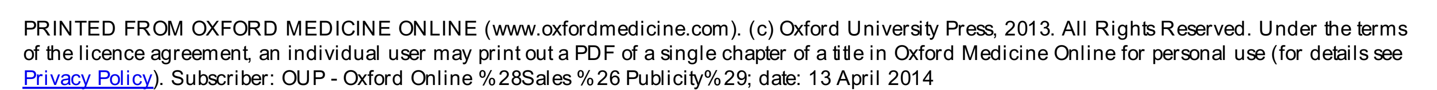
There are a number of hypersomnia syndromes that are defined by ICSD-2 as the inability to stay awake and alert during the major waking episodes of the day resulting in unintended lapses into drowsiness or sleep.[52] Excessive daytime sleepiness (EDS) can be associated with increased total sleep time and automatic behavior. The social ramifications for those who suffer from EDS include being called lazy, having difficulty completing school or maintaining a job, managing family responsibilities, and being at risk for accidents and injuries (Table 15–11).

Table 15–11 Subclassification of Hypersomnia
Narcolepsy with Cataplexy
Narcolepsy without Cataplexy
Narcolepsy due to a medical condition
Narcolepsy, unspecified
Other Hypersomnias
Recurrent Hypersomnia
Kleine-Levin Syndrome
Menstrual-Related Hypersomnia
Idiopathic Hypersomnia with long sleep time
Idiopathic Hypersomnia without long sleep time
Behaviorally Induced Insufficient Sleep Syndrome
Hypersomnia due to a medical condition
Hypersomnia due to a drug or substance
Hypersomnia not due to a substance or known physiological condition (Nonorganic Hypersomnia, NOS)
Physiological (Organic) Hypersomnia, unspecified (Organic Hypersomnia, NOS)

Hypersomnia syndromes may result from primary sleep disorders or secondary disorders due to medical conditions, side effects from medications or identifiable lesions within the hypothalamus, thalamus, and brainstem.

Narcolepsy with cataplexy is the most common and pathophysiologically best understood hypersomnia syndrome. It is an abnormality of excessive daytime sleepiness and dysregulation of REM phenomena. The clinical characteristics include excessive daytime sleepiness associated with automatic behavior, cataplexy or muscle atonia in the setting of emotional stimulus, hypnagogic hallucinations, sleep paralysis, and disrupted nocturnal sleep. It is not a disorder of excessive sleep, the total amount of sleep remains the same but the distribution of the sleep is altered.

Its estimated prevalence is 1 in 2000 individuals or 0.05%–0.067% in the United States.[158] The chance of an affected first degree relative has been estimated at only 1%–2%, but this is a higher rate than the general population. The age of onset has two peaks; one around the age of 15 and another in the mid thirties, but the time to diagnosis can be prolonged.[159] Not all patients have all the symptoms at once and some develop over time. A person may begin to have symptoms of EDS during young adulthood and develop hypnagogic hallucinations over the next few years, especially if not treated. It is not until classic cataplexy develops several years later that the diagnosis of



narcolepsy is even considered.

Understanding the regulation of REM phenomena is important in understanding the symptoms associated with narcolepsy. Cataplexy is a specific symptom that in emotional situations, patients lose tone in various body parts that can be as subtle as a slack jaw, to their knees buckling. Patients report maintained awareness of their surroundings, but are unable to respond due to the atonia. Strong emotions activate the PPT and stimulate the downstream projections to the spinal interneurons, which then inhibit the motor neurons in the spinal cord and result in the atonia.

When REM periods occur earlier as they do in narcolepsy and intrude into the waking or drowsy state, dream imagery also intrude and may be responsible for the apparent hallucinations that occur as patients are falling asleep. Sleep paralysis is described as the inability to move appendicular musculature on awakening. It is a frightening phenomenon that results from persistence of REM atonia upon waking but usually only lasts a few seconds to a few minutes. This symptom can also occur independently of a diagnosis of narcolepsy and has been associated with sleep deprived states as may be seen in severe sleep apnea syndromes.

Supportive testing includes an overnight polysomnogram to ensure an adequate night of sleep and to exclude any other sleep disorder such as sleep apnea prior to a multiple sleep latency test (MSLT). This test consists of a series of 4–5 nap opportunities and the latency to sleep onset and the number of sleep onset REM periods are noted. A short mean sleep latency of less that eight minutes and two or more sleep onset REM periods without any other condition that can account for such a phenomenon is consistent with a diagnosis of narcolepsy.

Pathophysiology

It is now recognized that narcolepsy with cataplexy is a disorder of the orexin (hypocretin) system. This group of cells resides within the lateral thalamus and modulates wakefulness via the TMN. In the canine model of narcolepsy with cataplexy, a nonfunctional orexin (hypocretin) receptor has been identified.[158,159] In the human disorder, it is suspected that orexin (hypocretin) cell loss may be the mechanism. Ninety percent of patients with narcolepsy with cataplexy have an orexin (hypocretin) CSF level below 110 µg/mL.[158] The loss of function in the oxrexin (hypocretin) system results in the EDS. Narcolepsy with cataplexy has been hypothesized to be an autoimmune disorder. The evidence to support this hypothesis is the association with a 90%–100% presence of the specific human leukocyte antigens, DQB1–0602(DQ1) with narcolepsy with cataplexy. In contrast in the general population the incidence is only 12%–38%.[159] A few autopsy studies have demonstrated loss of cells in the hypothalamus that are presumably orexin (hypocretin) cells. Furthermore there have been case reports of steroid use or intravenous immunoglobulin use improving the symptoms. However, no circulating autoantibodies against orexin (hypocretin) cells have been detected. There are case reports that intravenous immunoglobulins have been effective at the onset of the disorder.[160] Other down stream targets of the orexin (hypocretin) system such as receptor abnormalities may be abnormal in other forms of narcolepsy.

Rationale for treatment

American Academy of Sleep Medicine published their guidelines for the treatment of narcolepsy in 2000.[161] The goals of treatment of narcolepsy should rely on a combination of behavioral approaches and pharmacological agents targeting the clinical symptoms of excessive daytime sleepiness, cataplexy, and consolidation of nocturnal sleep to improve quality of life. Short scheduled naps can be refreshing for patients with narcolepsy and allow them to remain alert to complete a task or attend a function. Reviewing and addressing sleep hygiene can help consolidate nocturnal sleep without the use of any additional medications. Modafinil is recommended as first line treatment for EDS and stimulants can be used as second line. The dose administered should be the lowest effective dose and if necessary may need to be repeated during the day. Especially patients who are on stimulants should have regular follow up evaluations. The guidelines for the treatment of cataplexy with TCAs or SSRIs were suggestive but not conclusive. Sodium oxybate improves both EDS, cataplexy and improves nocturnal sleep architecture. Pharmacological management to improve fragmented nocturnal sleep has been achieved by the use of hypnotics. Although clonazepam was initially used, sodium oxybate may become the preferred agent in the treatment narcolepsy in general.

Future targets

Current management of narcolepsy with cataplexy targets the symptoms but does not target its underlying pathophysiology, which has not yet been fully elucidated. The targets for treatment were recently reviewed.[162] Since the discovery of the orexin (hypocretin) system, attempts at modulating this neuromodulator are currently limited by the lack of availability of an agonist and an effective route of administration. Case reports of improvement with immunomodulators near the onset of the disorder have been described, but persistent effects are not clear. With the success of sodium oxybate, it seems to improve all the symptoms of narcolepsy, but its abuse potential and short half life make it difficult to use. A longer acting preparation or alternative GABA-B agents without epileptogenic properties may be of interest. Armodafinil, the R-(-) isomer of modafinil may be a longer acting wake promoting agent. Investigations into stimulants without addictive potential are in the works. New agents such as the H3 autoreceptor antagonist may be useful to stimulate wakefulness. Newer antidepressants such as venlafexine with multiple mechanisms are promising. Atomoxetine, indicated for the treatment of attention deficit hyperactivity disorder, inhibits the reuptake of norepinephrine and needs to be studied further. Exploring the enhanced noradrenergic tone that inhibits REM structures during wakefulness may be a future target for preventing cataplexy.

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders (CRSD) results from persistence or recurrent patterns of sleep disturbance due to alteration of the circadian time keeping system, misalignment between the endogenous circadian rhythm, and exogenous factors that affect the timing or duration of sleep.[52] The circadian related sleep disruption leads to insomnia, EDS or both and the sleep disturbance is associated with impairment of social, occupational or other areas of functioning (Table 15–12). Sleep diaries and actigraphy provide supportive evidence in the diagnosis. Timed light exposure and melatonin are important component to the treatment of CRSD. The only condition that has FDA approved treatment is shift work sleep disorder (SWSD). The rest of the conditions are treated with off label agents.

Table 15–12 Subclassification of Circadian Rhythm Sleep Disorders
Primary Circadian Rhythm Sleep Disorders Circadian Rhythm Sleep Disorder, Delayed sleep phase type Circadian Rhythm Sleep Disorder, Advanced sleep phase type Circadian Rhythm Sleep Disorder, Irregular sleep-wake type Circadian Rhythm Sleep Disorder, Free running (non-entrained) type Circadian Rhythm Sleep Disorders due to a medical condition Primary (Organic) Circadian Rhythm Sleep Disorders, unspecified other physiological (organic) circadian rhythm, unspecified (organic circadian rhythm disorder, NOS)
Behaviorally Induced Circadian Rhythm Sleep Disorders Circadian Rhythm Sleep Disorder not due to a substance or known physiological condition, jet lag type Circadian Rhythm Sleep Disorder not due to a substance or known physiological condition, shift work type Circadian Rhythm Sleep Disorder not due to a substance or known physiological condition, delayed sleep phase type Circadian Rhythm Sleep Disorder not due to a substance or known physiological condition, unspecified (Nonorganic circadian rhythm sleep disorder, NOS) Other Circadian Rhythm Sleep Disorder not due to a substance or known physiological condition Other Circadian Rhythm Sleep Disorder due to a drug or substance

Anatomy

The intrinsic regulation for the circadian rhythm described earlier in this chapter rely on the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus to respond to both external and internal cues for the appropriate timing of sleep. There are “clock genes” that genetically determine the timing and duration of sleep.[163–167] Melatonin signals darkness and inhibits the SCN, which in turn inhibits the TMN and releases the VLPO from inhibition to initiate sleep.

The specific etiologies for circadian rhythm sleep disorders are varied and not well elucidated.

Based on this definition CRSDs can be divided into two categories based on alterations in the endogenous circadian rhythm regulators or the external environment (Figure **15–5**). Some people have preferences for certain time of the day (night owls and morning larks) but are able to get sufficient sleep and their daytime functioning is not impaired. In delayed sleep phase syndrome (DSPS) and advanced sleep phase syndrome (ASPS), examples of the endogenous rhythm misaligned from societal norms, result in difficulty with functioning warranting medical attention. If allowed, patients with DSPS have normal sleep periods; the timing is delayed so for an example they may sleep at 4:00am and not awaken until 12:00pm. When they try to get up to go to school and work, their total sleep time decreases and as a result they are tired during the day and may complain of insomnia because they have difficulty falling asleep. Characteristically adolescents fall into this sleep pattern. This condition is further potentiated by the lack of morning light exposure. A combination of melatonin five hours prior to the desired bed time and early morning light exposure with a light box can advance the sleep phase so that the patient can function normally.[168]

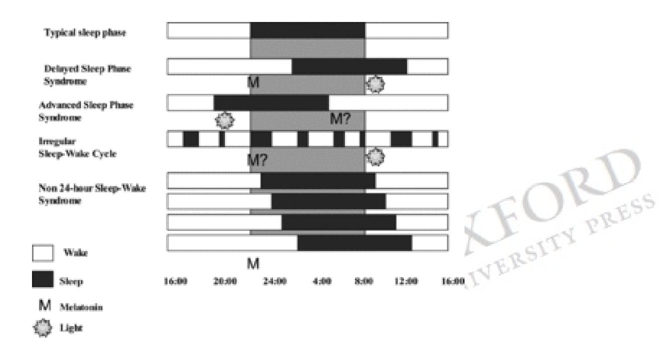


Figure 15–5.
Schematic of circadian phase in selected circadian rhythm sleep disorders. Delayed sleep phase syndrome results in chronic and stable delay of habitual sleep and wake times, whereas advanced sleep phase syndrome results in chronic and stable advance of habitual sleep and wake times. The irregular sleep-wake rhythm is characterized by at least three erratic sleep periods throughout the 24-hour day. The non-24-hour sleep-wake syndrome leads to a progressively delayed sleep period over time. Depending on the sleep disorder, the goal of therapy timing of melatonin and light therapy differs. Adapted from Fahey and Zee.[10]

In contrast, patients with ASPS complain of being unable to function in the evenings because they are excessively sleepy or of early morning awakenings. Typically older patients fall into this sleep pattern and exposure to bright light in the early evening may help delay the time they go to sleep and the normal sleep period delays the wake time appropriately. There is less evidence to suggest that melatonin in the morning helps to delay wake time.

The free running or nonentrained type of CRSD occurs in those who are blind and have no light perception. Their sleep wake period is determined by the intrinsic rhythm alone. They have normal sleep periods but their sleep onset time becomes progressively delayed until they become out of phase with the environment. These patients seem to be most sensitive to small doses of melatonin 1 hour prior to their desired bed time.[169]

Patients with developmental delay, traumatic brain injuries and dementia are at increased risk for irregular sleep wake cycles. Anterior hypothalamic lesions and damage to the SCN can result in the loss of regulatory mechanisms. The total sleep time may be normal, but it is scattered in short random naps throughout the 24-hour period. Regulating the patient’s daytime social schedule and light exposure and implementing sleep hygiene have been found to be helpful. Melatonin has been tried with variable results.

The second category of circadian rhythm sleep disorders is behaviorally induced by extrinsic factors. Jet lag has become a common phenomenon as rapid travel across three or more time zones has become easier. Not only do people complain of having difficulty adjusting to the appropriate sleep period, they also have difficulty with daytime functioning and have other systemic complaints such as headache, and GI symptoms. Traveling eastward tends to be more difficult, since the advancement of sleep is more difficult than the natural tendency to delay sleep. Exposure to morning light can alleviate some of the symptoms. Melatonin taken a few days prior to travel around the desired bedtime of the destination can also assist in the adjustment process.[170]

Fifteen percent of the working population or about six million people in the United States do some type of shift work.[171] There is an increased incidence of accidents and near misses in this population. Consequences of untreated SWSD have been associated with increased cardiovascular, gastrointestinal disease, anxiety and depression. When the sleep wake pattern is directly opposite from internal cues, patient have difficulty with excessive sleepiness during their wake period and insomnia during their sleep period.[172] Treatment should begin with behavior techniques such as adequate sleep hygiene, napping if allowed while at work and dark sunglasses during the day to avoid entrainment. The goals of pharmacological interventions should be to help initiate sleep or increase wakefulness. Melatonin may help initiate sleep and shift circadian rhythms but the results were variable.[173] Zolpidem in shift work improves the quality and quantity of sleep, but it may worsen mood.[174] Benzodiazepines also had mixed results. Amphetamines have been tried but the issues of tolerance and impairment of sleep limit its use. Modafanil is the only agent that has sufficient data to support its use. Despite its benefits, patients admit that their functioning was not as good as it would be if they worked a normal shift.[175]

Future targets

Current pharmacological treatments target sleep initiation and wake promotion. Novel targets could manipulate the SCN to adjust the intrinsic rhythm since the homeostatic drive is functioning normally. Melatonin agonists such as ramelteon should be further investigated in this line. Improving waking function with safer longer acting wake promoting agents such as armodafinil should also be pursued.

Parasomnias

According to ICSD-2 parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep or during arousal from sleep.[52] Primary parasomnias result from intrusions of one state into another resulting in inappropriate behaviors that come to medical attention especially if they result in dangerous behavior or injury. The behaviors are not under conscious control, may or may not be associated with dreaming, and can be complex in nature with seemingly purposeful albeit illogical actions. Behaviors described can be simple talking or walking to quite complex behaviors including preparing meals and eating and having sex without recall (Table 15–13). They are characterized by the state of sleep from which they arise: disorders of arousal, NREM or REM parasomnias. Secondary parasomnias are a behavioral expression of another organ system that occurs during sleep.

Table 15–13 Subclassification of Parasomnias
Disorders of Arousal (From Non-REM Sleep) Confusional Arousals Sleepwalking Sleep Terrors
Parasomnias Usually Associated with REM Sleep REM Sleep Behavior Disorder Parasomnia Overlap Disorder Status Dissociatus Recurrent Isolated Sleep Paralysis Nightmare Disorder
Other Parasomnias Sleep-Related Dissociative Disorder Sleep-Related Enuresis Sleep-Related Groaning (Catathrenia) Exploding Head Syndrome Sleep-Related Hallucinations Sleep-Related Eating Disorder Parasomnia, unspecified Parasomnia due to a drug or substance Parasomnia due to a medical condition



Most NREM parasomnias occur more frequently in children and tend to occur in families. Their occurrence can be exacerbated by other sleep disorders such as sleep apnea or RLS that cause frequent arousals and state changes. Histories are sufficient to make the diagnosis because typical behaviors are rarely recorded during monitoring but polysomnography may be helpful to exclude other sleep disorders. Increased arousals from slow wave sleep are consistent with the diagnosis. The majority are benign and self limited so treatments are targeted in minimizing their occurrence and ensuring safety. None of these disorders have any approved pharmacological therapy.

REM sleep behavior disorder (RBD) has received the most attention with regards to pathophysiology and treatment.[176–178] RBD is defined as the loss of atonia during REM sleep resulting in injurious, potentially injurious or disruptive behaviors.[52] As a result patients or their bed partners often present with significant injuries. Abnormal REM sleep behaviors can be documented during PSG monitoring in the absence of ictal EEG pattern during the behavior. Patients describe that they enact uncharacteristically aggressive dreams of being chased or fighting off attacker. The acute form of this disorder is frequently associated with substances that precipitate RBD including tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, selegiline, cholinergic agonists or caffeine abuse or result from withdrawal of a number of different substances including alcohol or barbiturates.[178] In chronic RBD, 80%–90% are men over the age of 50.[178] Their bed partners may describe a prodrome of sleep talking or twitching that may precede the diagnosis by 20 or more years. The chronic form can be idiopathic or secondary to other neurological disorders. The presence of RBD may precede the diagnosis of parkinsonian syndromes specifically the synucleinopathies by 10 years.[177] The association with narcolepsy may be related to the underlying problem with REM regulation and the medications used to treat narcolepsy may precipitate RBD.

Pathophysiology

Normally the states of wake, NREM and REM sleep are thought to be mutually exclusive. However, the transitions from state to state can fuse resulting in intermediary states that result in unusual behaviors. Normally the PPT and LDT are responsible for motor control during REM. Specifically the perilocus ceruleus region stimulates the nucleus reticularis magnocellularis in the medulla, which in turn inhibits the spinal neurons. But when the mesencephalic motor pattern generators are disinhibited, phasic motor activation allows RBD patients to enact their uncharacteristically aggressive dreams.[177] Cats with bilateral pontine lesions have REM without atonia and enact their aggressive dreams. One pathological study from a patient with RBD demonstrated depletion of neurons that had Lewy body inclusions in the region of the locus ceruleus; suggesting the association with parkinsonian syndromes and other synuceinopthies.[179] PET and SPECT scans suggest decreased binding in the presynaptic dopamine transporter system in the nigrostriatal system of the brainstem, but its relationship with RBD has not been clarified.[52]

Diagnosis is made by a combination of history, physical examination and polysomnographic findings. Additional EEG electrodes should be used to exclude the diagnosis of frontal lobe epilepsy and additional EMG electrodes demonstrate increased submental EMG tone or excessive phasic twitching. Otherwise the sleep architecture is normal. Video recording can document the behavior. A follow up MSLT should be done only if there is concern for excessive daytime sleepiness. If there are findings suggestive of a degenerative disorder, neuropsychological testing may identify symptoms of cognitive dysfunction even prior to the diagnosis of parkinsonism. Imaging studies are indicated by the constellation of symptoms.[178]

Treatment approach

The initial approach should be behavioral to maintain safety. However, when the behavior becomes more violent and results in injury, pharmacological management should be considered. Based on open label trials and clinical experience clonazepam is the treatment of choice. Low doses of 0.5–1.0 mg before bedtime are 87%–90% effective.[178] It suppresses locomotive centers and reduces the behavior without tolerance and the behavior relapses without medications. Melatonin in two open label trials restored REM atonia in five of the six subjects and in 15 subjects 3–9 mg of melatonin 30 minutes prior to sleep onset diminished tonic EMG during REM based on PSG.[180,181] The results seem less potent than clonazepam, but may represent an alternative or adjunctive treatment option. Pramipexole in two small case series improved in REM behaviors without any change to the PSG one with eight and the second in 10 subjects.[182–183] Alternative agents including TCAs, carbamezepine, gabapentin, clonidine, and L-dopa have been tried but there is not sufficient evidence for their efficacy.[178]

Future targets

Prior to speculating on future targets, future studies should be directed towards understanding the pathophysiology of complex motor control during sleep. If the behavior becomes injurious, then clonazepam is an effective medication, but it has its complications including daytime sedation, and poor tolerance especially an older population. Alternatives such as melatonin and pramipexole have been examined, but the value has not been demonstrated in large placebo controlled trials.

Sleep-Related Movement Disorders

During normal sleep, movement diminishes. Sleep-related movement disorders can be described as simple, stereotyped movements that disrupt sleep or sleep related monophasic movement disorder such as sleep related cramps (Table 15–14).[52]

Table 15–14 Subclassification of Sleep-Related Movement Disorders
Restless Legs Syndrome (including Sleep-Related Growing Pains) Periodic Limb Movement Sleep Disorder Sleep-Related Leg Cramps Sleep-Related Bruxism Sleep-Related Rhythmic Movement Disorder Sleep-Related Movement Disorder, unspecified Sleep-Related Movement Disorder due to a drug or substance Sleep-Related Movement disorder due to a medical condition

Leg cramps are characterized as a spasm of the muscles of the foot or calf and can wake patients out from sleep. Massaging the muscle relieves the cramp. Laboratory studies may reveal electrolyte abnormalities. Bruxism due to increased tone of the masseters and other muscles of the jaw result can result in headaches. Dentists find evidence of worn surfaces of the teeth and can make mouth guards to prevent further injury. Some children have rhythmic and rocking movements prior to falling asleep. These movements can be as simple as head rocking to elaborate as head banging. The rhythmic nature of these movements can be misinterpreted as seizures.

Restless leg syndrome is the only sleep related movement disorder that has FDA approved treatments. The International RLS study group developed standardized criteria (Table 15–15)[108] for the diagnosis of RLS and the ICSD-2 incorporated into its definition. Due to the sensitivity to dopamine agonists, response to dopamine agonist treatment has become a secondary criterion for the diagnosis. Although clinical history is sufficient for the diagnosis, periodic limb movements of sleep (PLMS) noted on PSG are seen in 80%–90% of cases.[184] Patients come to medical attention because they complain of difficulty initiating and maintaining sleep and often present to a sleep medicine physician for the evaluation of insomnia.

Table 15–15 International RLS Criteria
Essential Criteria 1. Urge to move, associated with sensory discomfort in the legs 2. Symptoms begins or worsens during restful periods 3. Partly or totally relieved by movement such as walking, bending, stretching 4. Only occur or becomes worse in the evening or at night
Supportive Criteria 1. Response to dopaminergic treatment 2. Presence of periodic limb movements during wake or sleep
Family history of RLS inherited in autosomal dominant fashion

Restless leg syndrome is a common disorder that can affect from 2%–15% of the adult population, increases in frequency with age, and tends to affect women more frequently.[185] The disorder is often idiopathic and familial. Observational studies of large families have suggested an autosomal dominant inheritance pattern and several genes have now been identified from large kindreds. There are numerous secondary causes. The most common is the association with iron deficiency states such as pregnancy and end stage renal disease with uremia. Restless leg syndrome has also been associated with rheumatoid arthritis, fibromyalgia, peripheral neuropathies or radiculopathies, and Parkinson's disease. Certain compounds can exacerbate RLS such as nicotine, caffeine, SSRIs, metochlopramide, prochlorperazine, dopamine antagonists, diphenhydramine, and alcohol.

Anatomy

Numerous lines of investigation point to a central nervous system mechanism that involves iron metabolism and the dopaminergic system. Functional imaging with SPECT and PET scans suggest that there is decreased striatal dopamine binding.[186] Pathological specimens have demonstrated low iron levels in the CNS and can be manifested as low CSF ferritin levels and elevated transferrin levels. Ferritin is an essential cofactor for tyrosine hydroxylase in the rate limiting step of dopamine production. One potential region that is currently a focus of research is a group of dopminergic neurons that reside in the midbrain and project caudally to the spinal cord. These neurons are in close proximity to the hypothalamus, which may explain the circadian nature of this disorder.[187]

Treatment approach

The initial approach (Figure **15–6**) should be to review exacerbating factors and eliminate them. Then work up for secondary causes and the treatment of those disorders should take priority. If symptoms are intermittent of situational, such as sitting for prolonged periods at a theater or a trip, behavioral approaches such as light exercise or short acting levodopa is recommended. In 2004 the AASM reviewed the data and developed practice parameters for the use of dopamine agonists for moderate to severe RLS.[188] At that time levodopa was considered standard of treatment but tolerability was limited by rebound and augmentation. Since then ropinirole and pramipexole have been approved based on stronger evidence from randomized controlled trials and have fewer side effects and less augmentation. If a patient is unable to tolerate one agent switching to another may still be of benefit. If a patient cannot tolerate a dopamine agonist or they have a painful component to their symptoms, an anticonvulsant or a low potency opioid can be used. Benzodiazepines and high potency opioids are reserved for treatment resistant RLS. Despite the extensive review of the available literature, the AASM did not make any recommendations for children, pregnant women or patients with renal insufficiency, all special populations who are more prone to this disorder.

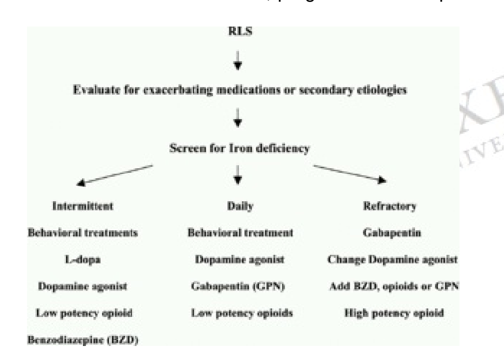


Figure 15–6.
Treatment algorithm for RLS. Adapted from Silber.[189]

Future targets

Increasing knowledge of the pathophysiology behind RLS can lead to development of specific dopamine receptors agonists. Understanding how augmentation occurs can help to avoid this limiting side effect. Provide symptomatic relief by improving pain control without issues of tolerance and dependence. Current medications available that improve sleep consolidation have deleterious effects on sleep architecture, so better tolerated agents are needed. Finding treatment options for vulnerable patient populations such as pregnant women, children and patients with renal insufficiency needs to be explored.

Conclusion

Understanding the anatomy and neurophysiology of sleep leads to an appreciation for the intricate control ofwaking and sleep regulation.

There is much opportunity for some systems to fail and result in sleep disorders. Understanding this information can be translated into the clinical treatment of sleep disorders. By manipulating these neurotransmitter systems, pharmacological agents can enhance or reduce the desired state. The goal is to tailor the target to reduce unwanted side effects that limit current therapeutic options. Further study into this field will result in more precise treatment options.

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Therapy of Central Nervous System Infections

Chapter: Therapy of Central Nervous System Infections
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The ability to identify the causative organism of a central nervous system infection (CNS) has been significantly improved over the last several years due to the availability of new molecular diagnostic techniques. The therapy of CNS infections and the prevention and treatment of their neurological complications has not yet benefited from the advances in diagnosis. There are an increasing number of community acquired bacterial organisms that are resistant to antibiotics, therefore the therapy of these infections must be guided by antimicrobial sensitivity testing. Patients that survive bacterial meningitis, herpes encephalitis, fungal, or tuberculous meningitis often have persistent neurological deficits affecting memory, gait and vision. The role of adjunctive agents in the therapy of these infections is being investigated in animal models and clinical trials. The therapy of CNS infections is intermittently interrupted and complicated by the adverse effects of the antimicrobial agents used to eradicate the infection. Antituberculous agents cause hepatotoxicity, peripheral neuropathy, and optic neuritis. Antifungal agents cause nephrotoxicity, hepatotoxicity and bone marrow suppression. When hydrocephalus develops in the course of fungal meningitis requiring the insertion of a ventriculoperitoneal shunt, multiple shunt revisions may be necessary before the patient improves.

The current therapeutic recommendations for CNS bacterial, viral, fungal, and parasitic infections will be reviewed, the complications of therapy and controversies discussed, and alternatives to best initial management provided for those patients who cannot tolerate first line therapy or who have resistant organisms.

Lumbar puncture

Treatment of most CNS infections depends heavily on data collected from brain imaging and lumbar puncture. Lumbar puncture should be performed only after a careful neurological examination and evaluation of platelet count and INR. Platelet count less than 50,000, prolonged prothrombin time or partial thromboplastin time or recent use of low-molecular weight heparin present an increased risk of spinal epidural or subdural hematoma after lumbar puncture, which could lead to paralysis.[1] Infection in the subarachnoid space that would require passing the needle through the infection is a contraindication.[2] Clinical findings of altered consciousness, focal neurological deficits, sluggishly reactive or nonreactive pupils, posturing, abnormal eye movements, Cushing reflex, and papilledema warrant further evaluation with neuroimaging before a lumbar puncture can be performed.[1] Many authorities have recommended routine brain imaging before lumbar puncture to reduce the risk of cerebral herniation.[3] Although brain computed tomography (CT) can accurately predict which patients are at risk for herniation,[4] some studies suggest that a normal neurological exam, including normal level of consciousness, predicts a benign brain CT and thus a low risk of herniationA[6] Hasbun and colleagues showed that patients who are under the age of 60 and immunocompetent with no neurological deficits, no history of CNS disease, and no seizures within one week of presentation had a low risk of brain CT abnormalities.[5] However, despite this conservative approach, 3% of patients meeting the above criteria still had abnormal head CT. The available literature suggests that a normal neurological examination in a select subgroup of patients does reduce, but not necessarily eliminate the risk of herniation from a lumbar puncture. All patients that do not meet the above

criteria should have a CT scan of the brain before lumbar puncture is performed. Further studies will help to better identify which patients can safely have a lumbar puncture without a CT scan.

Bacterial meningitis

Empirical Antibiotic Therapy

In a patient with clinical signs and symptoms suggestive of acute bacterial meningitis, antibiotic therapy should begin immediately after drawing blood cultures for Gram's stain and bacterial culture.[7] The choice of antibiotic therapy is influenced by the patient's age, predisposing factors, underlying diseases, and the most probable meningeal pathogen (Table 16–1).

Table 16–1 Empirical Therapy for Bacterial Meningitis

Population/Etiology	Microorganism(s)	Treatment
Newborns	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes*	Cefotaxime plus ampicillin
Infants and children	*Neisseria meningitidis, Streptococcus pneumoniae, Hemophilus influenzae**	Ceftriaxone or cefotaxime plus vancomycin plus dexamethasone
Healthy, immunocompetent adults (younger than age 50): community acquired	*S. pneumoniae, N. meningitides*	Ceftriaxone, cefotaxime or cefepime plus vancomycin plus dexamethasone
Neurosurgical patient, or hospital-acquired	Gram-negative bacilli, including *Pseudomonas aeruginosa, staphylococci*	Ceftazidime or meropenem plus vancomycin
Shunt infection	Coagulase negative staphylococci, *Staphylococcus aureus*	Vancomycin
Adult older than 50 years of age, immunocompromised (see text below)	*L. monocytogenes*, gram-negative bacilli, including *P. aeruginosa, Streptococcus pneumoniae*	Ceftazidime or meropenem plus ampicillin plus vancomycin plus dexamethasone

* incidence has declined since the introduction of *H. influenzae* type b conjugate vaccine.

In newborns, the most common causative organisms of bacterial meningitis are *Streptococcus agalactiae* (group B streptococcus), *Escherichia coli*, and *Listeria monocytogenes*. Empiric therapy of bacterial meningitis is neonates, includes a combination of a third-generation cephalosporin and ampicillin. *Neisseria meningitidis* and *Streptococcus pneumoniae* are the most common meningeal pathogens in infants and children with community-acquired bacterial meningitis in the United States.[8] Worldwide, *Hemophilus influenzae* is a major cause of bacterial meningitis in infants and children, however, the incidence has declined in the United States and other industrialized countries due to the routine use of the *Hemophilus influenzae* type b (Hib) conjugate vaccine.[9,10] *N. meningitidis* and *S. pneumoniae* are also the most common causative organisms of community-acquired bacterial meningitis in immunocompetent adults, and these organisms are increasingly resistant to penicillin and the cephalosporins. Empiric therapy of bacterial meningitis in children and adults should be based on the possibility that penicillin and cephalosporin-resistant pneumococci are the causative organisms of the meningitis, and include a third or fourth generation cephalosporin, either ceftriaxone (pediatric dose: 100 mg/kg/day in a 12-hour dosing interval; adult dose: 2 gm every 12 hours) or cefepime (pediatric dose: 150 mg/kg/day in an 8-hour dosing interval; adult dose: 2 gm every 12 hours) plus vancomycin (pediatric and adult dose: 40–60 mg/kg/day in a 6- or 12-hour dosing interval). Individuals who are 50 years of age or older, and those who are immunocompromised due to organ transplantation, cancer, immunosuppressive therapy, chronic disease (diabetes), pregnancy, alcoholism, or corticosteroid therapy are at risk for meningitis caused by *Listeria monocytogenes*. Ampicillin (2–2.5 grams every 4 hours) is added to the empiric regimen for patients at risk for *L. monocytogenes* infection. Gram-negative bacilli and staphylococci are the most common causative organisms of bacterial meningitis in the patient who has undergone a neurosurgical procedure, with the exception of insertion of a shunt. Coagulase-negative staphylococci and *Staphylococcus aureus* are the most common pathogens causing shunt infections (see Table 16–1). Empiric therapy of meningitis in the postneurosurgical patient should include a combination of vancomycin and either ceftazidime or meropenem.[11]

Specific Antibiotic Therapy

After the causative organism is identified, therapy should be modified based on antimicrobial sensitivity testing. Duration of antibiotic therapy depends on the organism and the clinical response to treatment. Uncomplicated *N. meningitidis* meningitis can be treated with intravenous antibiotics for 4 to 7 days. However, meningitis due to *S. pneumoniae, H. influenzae*, and group B streptococci requires 10 to 14 days of intravenous antibiotics and *L. monocytogenes* meningitis requires 3 to 4 weeks of intravenous antibiotics.[11]

Patients with suspected *N. meningitidis* meningitis should be in respiratory isolation for 24 hours after initiation of intravenous antibiotics. Any person that has had close contact with the patient from the onset of the disease should receive chemoprophylaxis (Table 16–2).[11–14] Rifampin 10 mg/kg (up to a maximum of 600 mg) orally every 12 hours for two days has been the therapy of choice in the past. However, the use of rifampin during pregnancy is contraindicated and there is evidence for resistance to rifampin in outbreaks of *N. meningitidis* meningitis. Ceftriaxone as a single dose of 125 mg in children and 250 mg in adults is an appropriate alternative, but it must be given parenterally. Ciprofloxacin 500 mg orally as a single dose is another alternative in adults, but is not approved for routine pediatric use. Patients with meningitis due to pathogens other than *N. meningitidis* do not require isolation or prophylaxis for close contacts.

Table 16–2 Dosing of Antimicrobial Agents for Prophylaxis of Bacterial Meningitis

Age	Antimicrobial Agent	Dosing
Infants <1 month	Rifampin	5 mg/kg every 12 hours orally for two days
Infants ≥1 month	Rifampin	10 mg/kg every 12 hours orally for two days
Children	Ceftriaxone or	125 mg once IM or IV
	Rifampin	10 mg/kg every 12 hours orally for two days
Adults	Ceftriaxone or	250 mg once IM or IV
	Ciprofloxacin or	500 mg once orally
	Rifampin	600 mg every 12 hours orally for two days



Adjunctive Therapy

Multiple studies have demonstrated reduced mortality and neurological sequelae in bacterial meningitis with the use of corticosteroids. A recent Cochrane review showed the benefit of using dexamethasone in children and adults with acute bacterial meningitis regardless of the causative organism.[15] Although some of the studies do not show statistically significant improvement of outcomes, the overall trend is in favor of using dexamethasone for acute bacterial community-acquired meningitis of any etiology.[15] There are insufficient studies in patients with CSF shunts, patients who have had neurosurgical procedures, and patients with hospital-acquired meningitis to determine if corticosteroids are beneficial.[16,17]

With regard to timing of corticosteroid use, the available studies show a clear benefit for initiating dexamethasone therapy just before or with the first dose of intravenous antibiotics.[16] Although not directly studied, the benefit of dexamethasone therapy appears to decline with time from initial antimicrobial dosing.[16] The dose of dexamethasone has differed among studies, but a dose of 0.4–0.6 mg/kg/day in children and 40 mg/day in adults divided every six hours has been demonstrated to be efficacious.[15,16] Most studies continued dexamethasone for four days of therapy.[16] One study compared two days of dexamethasone to four days in children and found equal efficacy. However, the physicians in this study were not blinded so the results should be interpreted with caution. Current recommendations are to start dexamethasone in all patients with suspected community-acquired meningitis before or with the first dose of intravenous antibiotics. Patients that have already received multiple doses of intravenous antibiotics and patients with hypersensitivity to steroids, CSF shunt, recent neurosurgical procedure, or hospital acquired meningitis should not receive steroids routinely.[16] The recommended dose of dexamethasone is 0.1–0.15 mg/kg every six hours in children and 10 mg every six hours in adults and this should be continued for four days in cases of confirmed bacterial meningitis regardless of the causative microorganism.

Bacterial abscess and empyema

Bacterial Abscess

Before an abscess forms, seeding of the brain parenchyma with bacteria will cause a localized cerebritis. Treating a brain infection at this stage may be successful with antibiotics alone. However, once an abscess is formed, optimal therapy requires a combination of antibiotics and surgical intervention. At presentation, if brain imaging indicates an abscess that would be amenable to neurosurgical intervention, the patient should have CT-guided stereotactic aspiration of the abscess immediately without antibiotic pretreatment.[18] In patients that are not good surgical candidates, or in patients where the abscess is located in deep or eloquent parts of the brain, empirical antibiotics are started and surgical aspiration is deferred.[19] When antibiotics and aspiration do not control the infection, excision of the abscess can be a definitive treatment. Excision is used only when less invasive techniques have failed because of the risk for permanent neurological deficit with surgery. Excision is contraindicated when the abscess is located in deep or eloquent parts of the brain.

Empirical antibiotics should be started after aspiration of the abscess or immediately at the time of diagnosis in patients that are not candidates for aspiration. Empirical therapy includes a third-generation or fourth-generation cephalosporin, vancomycin, and metronidazole (Table 16–3). These antibiotics offer coverage for most of the potential bacterial pathogens associated with abscesses regardless of the underlying cause. If the source of the abscess is known, empirical antibiotics can be modified to cover the most common pathogens in the specific subgroup. Sinusitis-associated abscesses are usually caused by streptococci and anaerobes, but can be caused by *Hemophilus* species as well. In sinusitis-associated abscesses, empirical antibiotics consist of metronidazole for anaerobic coverage and either penicillin G for streptococcus coverage or a third-generation or fourth-generation cephalosporin to cover both streptococci and *Hemophilus* species. In otitis-associated abscesses, the most common causative organisms are streptococci, enterobacteriaceae, *Pseudomonas aeruginosa*, and *Bacteroides* spp. Empirical therapy of otitis-associated abscesses includes penicillin G for streptococci, metronidazole for *Bacteroides* species, and ceftazidime for enterobacte riaceae and *Pseudomonas aeruginosa*. A brain abscess from penetrating head trauma is most commonly caused by *Staphylococcus aureus, Clostridium* species, and enterobacteriaceae. Empirical therapy of abscesses due to penetrating head trauma includes a third-generation or fourth-generation cephalosporin and vancomycin. A brain abscess that occurs as a complication of a neurosurgical procedure is usually caused by staphylococci, enterobacteriaceae, or *Pseudomonas* species. Empirical antimicrobial therapy for an abscess complicating a neurosurgical procedure should include vancomycin for staphylococcus coverage and either meropenem or ceftazidime for coverage of enterobacteriaceae and *Pseudomonas* sp.[18]

Table 16–3 Empirical Therapy for Bacterial Abscess and Empyema

Population/Etiology	Microorganism(s)	Treatment
Unknown etiology	Streptococci, anaerobes, *Hemophilus* spp., enterobacteriaceae, *P aeruginosa, Bacteroides* spp., *S. aureus, Clostridium* spp.	Third-generation or fourth-generation cephalosporin plus vancomycin plus metronidazole
Sinusitis-associated	Streptococci, anaerobes, *Hemophilus* spp.	Metronidazole plus either penicillin G or a third-generation or fourth generation cephalosporin
Otitis-associated	Streptococci, enterobacteriaceae, *P. aeruginosa, Bacteroides* spp.	Metronidazole plus penicillin G plus ceftazidime
Penetrating head trauma	*S. aureus, Clostridium* spp., entero bacteriaceae	Third-generation or fourth-generation cephalosporin plus vancomycin
Post-neurosurgery	Enterobacteriaceae, *Pseudomonas* spp., staphylococci	Vancomycin plus meropenem or ceftazidime

Once the causative microorganism is identified, the antibiotic regimen can be narrowed to target the specific bacteria as shown in Table 16–4. All antibiotics are given intravenously and should be continued for six to eight weeks. A head CT or MRI should be performed at least every two weeks to follow the progress of treatment. If the abscess enlarges after two weeks of intravenous antibiotics or fails to decrease in size after four weeks of antibiotic treatment, further neurosurgical intervention is required.[20] A brain abscess caused by *Nocardia asteroides* requires 6 to 12 months of trimethoprim-sulfamethoxazole. A *Nocardia* abscess usually requires complete excision to obtain a cure (Table 16–4).

Table 16–4 Antibiotics for Specific Bacteria in Brain Abscess or Empyema (Recommendations are in Bold)

Pathogen	Antibiotic
Bacteriodes fragilis	**Metronidazole 2000 mg/day (500 mg every six hours)**
Enterobacteriaceae *(e.g., Klebsiella, E. coli, Proteus)*	**Ceftriaxone 4 grams/day (2 g every 12 hours)** or **Cefotaxime 12 grams/day (2 g every four hours)** or **Cefepime 4 grams/day (2 g every 12 hours)** or Meropenem 6 grams/day (2 g every eight hours)
Hemophilus influenzae	**Ceftriaxone or cefotaxime**
Nocardia asteroides	**Trimethoprim-sulfamethoxazole 15–20 mg/kg per day of TMP component (5–6.67 mg/kg every eight hours)**
Pseudomonas aeruginosa	**Meropenem** or cefepime or ceftazidime 6 g/day (2 g every eight hours)
Staphylococci Methicillin-susceptible Methicillin-resistant	**Nafcillin or oxacillin 12 g/day (2 g every four hours or 3 g every six hours)** **Vancomycin 45–60 mg/kg/day (every 6 or 12 hour dosing interval)**
Streptococcus spp.	**Penicillin G 20–24 million units/day (3–4 million units every four hours)** or **ceftriaxone or cefotaxime or cefepime**

Corticosteroids can lead to decreased antibiotic penetration into the abscess and slow the formation of the abscess wall, so they should be avoided if possible. In patients with increased intracranial pressure, mass effect, or significant edema, a short course of corticosteroids can provide benefit.[21] Dexamethasone 10 mg every six hours for three to seven days is the recommended dosing. Seizures occur in approximately 50% of patients during the initial hospitalization and in 70% of patients after discharge.[22] Patients should be treated routinely for two years with antiepileptics to prevent seizures. If patients are seizure-free for two years, the antiepileptic medication can be discontinued.[18]

Intracranial Epidural Abscess and Subdural Empyema

Empirical therapy for an epidural abscess or subdural empyema is the same as for an intra parenchymal abscess of unknown etiology—a third-generation or fourth-generation cephalosporin, vancomycin, and metronidazole. Surgical evacuation is required for a cure and should be performed immediately. Intravenous antibiotics specific to the isolated organism should be continued for four to six weeks, followed by two to three months of oral antibiotics for an epidural abscess. For a subdural empyema, patients should receive three to four weeks of intravenous antibiotics followed by oral antibiotics to complete a six week course.[18]

Perinatal infections

Cytomegalovirus

Of newborns with intrauterine cytomegalovirus (CMV) infection, only about 10% are symptomatic at birth and the remaining 90% have a 10%–15% lifetime risk of sensorineural hearing loss.[23–26] The Collaborative Antiviral Study Group (CASG) and the National Institutes of Allergy and Infectious Diseases (NIAID) conducted a prospective, randomized, controlled trial of intravenous ganciclovir in symptomatic newborns with CMV infection. Their results showed a significant beneficial effect on hearing

outcome at six months and 12 months follow-up in the ganciclovir-treated group versus the no-treatment group. There was also a statistically significant increase in adverse effects of ganciclovir, especially neutropenia, though none of the ganciclovir-treated patients died from complications of the drug.[27] Foscarnet and cidofovir have been studied in CMV disease, but not in neonatal CMV, so the effectiveness of these drugs in neonatal CMV is unknown.

Herpes Simplex Virus

Neonatal herpes simplex virus (HSV) infection can be classified into three categories: mucocutaneous infection, disseminated infection, and infection of the central nervous system. Neonates with disseminated disease or CNS involvement have higher morbidity and mortality, but neonates with localized mucocutaneous infections can also have long-term neurological complications.[28] Symptoms usually develop in the second to third weeks of life and the disseminated and CNS infections can mimic other neonatal viral and bacterial infections.[29] Therefore, antiviral therapy should be initiated empirically as soon as an infection is suspected. In 1991, the CASG showed acyclovir to be the best option for treating all forms of neonatal HSV[30] In 2001, the CASG conducted a trial of high-dose acyclovir (60 mg/kg/day for 21 days) to compare this to the previous standard (30 mg/kg/day for 10 days). The trial participants were all given the high-dose acyclovir and the controls were taken from the previous CASG trial. This study showed a significant increase in survival and comparable normal development at 12 months in participants with disseminated disease or CNS involvement when receiving the high-dose acyclovir compared to the subjects in the previous CASG trial. The only reported side effect of the high-dose acyclovir was neutropenia, which resolved spontaneously during treatment or upon completion of the 21-day course without long-term sequelae.[31] Based on these studies, the current recommendations are to treat newborns with disseminated or CNS HSV infections with acyclovir 20 mg/kg every eight hours intravenously for 21 days.

Although a small percentage of neonates with only mucocutaneous involvement will later develop neurological complications, current recommendations do not include treating this population with acyclovir. Ongoing studies are evaluating whether prophylactic oral antiviral medications will lower the risk of neurological complications in infants with recurrent mucocutaneous eruptions. Other studies have addressed the prevention of transmission of HSV from mother to newborn. Several studies gave pregnant women oral antiviral medications during the last few weeks of pregnancy, resulting in fewer HSV lesions, but because of the low rate of vertical transmission, there was no effect on newborn outcomes.[32] The American College of Obstetricians and Gynecologists recommended prophylactic antiviral therapy in women with primary HSV infection during pregnancy and considering treatment in pregnant women with a history of recurrent genital herpes.[33]

Varicella-Zoster Virus (VZV)

Newborn varicella infection is manifested in two ways—congenital varicella embryopathy in which the fetus was exposed in utero and is born with congenital anomalies; and neonatal infection in which the newborn is exposed in the perinatal period. Infants born with congenital embryopathy do not require specific antiviral therapy because the effect of the virus has already been manifested.[34] Infants born to mothers with chicken pox in the days just prior to delivery are at a higher risk of contracting neonatal varicella either in the form of chicken pox or a severe, disseminated illness.[35,36] This population requires treatment with acyclovir 20 mg/kg every eight hours intravenously for 7 to 14 days.[37] Asymptomatic, exposed newborns should be monitored for 21 to 28 days in airborne and contact isolation either in the hospital or at home.[38] Prophylaxis with varicella-zoster immune globulins or with acyclovir has been recommended in the past, but there are insufficient data to make a standard recommendation.[39] Since term infants who are exposed to VZV, but are asymptomatic at birth, have a relatively benign illness, the use of prophylactic medications should be determined on a case-by-case basis.

Nonpolio Enteroviruses

Neonates are rarely infected with enteroviruses in utero. More commonly, children and adults transmit disease to infants either at birth or during the first month of life.[40,41] Enteroviruses are a frequent cause of benign aseptic meningitis in children and adults, but infants usually present with mild systemic symptoms such as poor feeding, fever, irritability, and lethargy.[38,42] Occasionally, the symptoms can be more severe including encephalitis, hepatitis, myocarditis, and sepsis.[43] Pleconaril has been shown to be effective in reducing the duration of headache in children and adults with enterovirus meningitis.[44,45] One case series of six neonates reported good outcomes in four of the six subjects. The two neonates with a poor outcome did not receive treatment until day nine of illness and each received only 7.5 mg/ kg per day of pleconaril for seven days. The four neonates with good outcomes all received 15 mg/kg/day for 10 days and treatment was initiated on days four or five.[45] Another series of four preterm neonates reported good outcomes in all four subjects. All of these neonates received 15 mg/kg/day for 7 to 10 days starting on days four to seven of illness.[46] Although these series are small, the use of pleconaril appears promising for neonatal enteroviral infection and warrants further investigation. The use of pleconaril should be considered in all neonates with confirmed enterovirus infection and clinically severe disease. Pleconaril should be initiated as soon as the diagnosis is made and given in a dose of 5 mg/kg orally every eight hours for 10 days.

Lymphocytic Choriomeningitis Virus

There is no specific treatment for lymphocytic choriomeningitis virus (LCMV) infections. Infected infants should receive appropriate supportive care and shunting of hydrocephalus when warranted. Prevention of LCMV is important and pregnant women should be advised to avoid contact with all rodents.

Rubella

Manifestations of the congenital rubella syndrome include sensorineural hearing loss, microcephaly, chorioretinitis, and intrauterine growth retardation.[47–50] The Centers for Disease Control and Prevention data from the 1980s through the 1990s show a clear association between increased rubella immunizations and decreased rates of congenital rubella syndrome.[51–53] In the United States and many other countries, routine vaccination of children is strongly recommended or required. Reportedly, more than 1000 women worldwide have been vaccinated inadvertently during pregnancy without a single reported case of congenital rubella syndrome.[54] Nevertheless, immunization during pregnancy remains contraindicated[55] and unimmunized pregnant woman should be counseled about the risks to the fetus if she were exposed to rubella.

Toxoplasmosis

Toxoplasmosis infection in pregnancy is usually asymptomatic in the mother. The effect on the fetus often results in miscarriage. If however, a pregnant woman is known to have contracted toxoplasmosis and the fetus is still viable, she should receive therapy to prevent transplacental infection of the fetus. Therapy consists of spiramycin 3g/day until delivery or the parasite is eradicated. If there is ultrasound or amniocentesis evidence of fetal infection, the mother receives sulfadiazine (50–100 mg/kg/day up to a maximum of 6g/day) and pyrimethamine (0.5–1 mg/kg/day up to a maximum of 100 mg/ day) with folinic acid supplementation to minimize toxicity. This regimen and a regimen of spiramycin 3g/day are alternated every three weeks. Congenital or perinatal toxoplasmosis infection should be treated for 12 months with similar three week alternating courses of sulfadiazine plus pyrimethamine (in the same doses as above) and spiramycin 100 mg/kg/day.[38]

Viral meningitis

Numerous viruses cause a meningitis syndrome characterized by headache, fever, nuchal rigidity, and inflammatory CSF changes. The herpesviruses, enteroviruses, arthropodborne viruses (arboviruses), lymphocytic choriomeningitis virus, mumps virus, and adenovirus all cause a nonspecific viral meningitis and are indistinguishable from one another clinically. A diagnosis of viral meningitis is usually made initially by history, physical exam lacking features of encephalitis, and characteristic CSF abnormalities of a lymphocytic pleocytosis. In cases where there is no evidence of focal neurological deficits, seizure activity, altered level of consciousness or papilledema, empirical therapy consists of only symptomatic treatment. Headache is often initially improved by lumbar puncture, but then returns and can be treated with nonsteroidal anti-inflammatory medications and amitriptyline.[56]

If a specific virus is identified, and an antiviral agent available, therapy can be directed toward that virus ifwarranted. Pleconaril has been used in enteroviral meningitis with

good results. In one double-blinded, placebo-controlled trail of 130 patients between the ages of 14 and 65 years with enteroviral meningitis, the group receiving 200 mg of pleconaril three times daily had a shorter duration of headache and returned to work or school faster than the group receiving placebo.[57] A double-blinded, placebo-controlled study of 221 children between ages 4 and 14 showed similar benefits of pleconaril with a dose of 2.5 to 5 mg/kg three times daily for seven days.[58] A third study of the compassionate-use program of pleconaril in patients with immunodeficiency or otherwise life-threatening enteroviral infection showed a clinical improvement in the majority of children receiving 5 mg/kg three times daily for 7 to 10 days and adults treated with 400 mg of pleconaril three times daily for 7 to 10 days.[45] Pleconaril is not routinely available, but can at times be obtained for compassionate use. Because pleconaril is specifically an antipicornavirus medication, it does not appear to be effective against other forms of viral meningitis.

The therapy of meningitis due to herpes simplex virus has not been defined by clinical trials. Parenteral and oral antiviral therapy shortens the duration of viral shedding and the duration of symptoms. The majority of patients are treated with oral, rather than parenteral, antiviral agents, either acyclovir (200 mg five times daily), valacyclovir (1000 mg twice daily) or famciclovir (500 mg three times daily) for 7 to 10 days. Herpes simplex virus-2 is a common causative organism of recurrent lymphocytic meningitis. In patients with recurrent episodes of fever and headache and a CSF lymphocytic pleocytosis, send CSF for PCR for HSV-2 DNA and serum IgM antibodies for HSV. One or the other or both may be positive, and antiviral therapy can be prescribed. When future episodes occur, the patient can be started on antiviral therapy without repeating spinal fluid analysis.

Fungal meningitis

Hundreds of species of fungi can cause disease in humans, but only a few occur on a routine basis in clinical practice. The most common fungi to cause meningitis are *Cryptococcus neoformans, Histoplasma capsulatum*, and *Coccidioides immitis*.

Antifungal Agents

In general, CNS fungal infections are treated with three classes of antifungal medications: (1) antifungal polyenes including amphotericin B (Fungizone), amphotericin lipid complex (Abelcet), amphotericin liposomal (Ambisome); (2) antifungal antimetabolite including flucytosine; and (3) antifungal azoles including fluconazole, itraconazole, ketoconazole, voriconazole. Amphotericin B was the first major antifungal medication and with its broad coverage, it is still the first choice for the treatment of many fungi. Intravenous amphotericin has a high incidence of adverse effects, especially nephrotoxicity. Side effects can be reduced by using one of the several available lipid formulations of amphotericin (Abelcet or Ambisome). In 2003, a review of seven studies demonstrated a significantly lower nephrotoxicity and equal efficacy of lipid formulations of amphotericin B compared to amphotericin B deoxycholate.[59] The limiting factor for the use of the lipid formulations in most institutions is the significant increase in cost of lipid formulations, which can be more than 100 times as expensive as amphotericin B deoxycholate.[60] Intrathecal amphotericin B has been used to maximize the amount of amphotericin in the CSF and limit systemic side effects. However, due to the high incidence of severe adverse effects, including arachnoiditis, cerebral vasculitis, and secondary bacterial infections, the use of intrathecal amphotericin is reserved for severe fungal infections that are resistant to intravenous and oral therapies.[61–64]

Flucytosine is an antifungal medication whose exact mechanism of action is not fully known. In fungal cells, the drug is converted to 5-fluorouracil, which inhibits nucleic acid synthesis. Although effective, early studies showed rapid fungal resistance to flucytosine when used alone, so it should be used only in combination with other antifungal medications.[65] Specifically, the combination of amphotericin B and flucytosine is recommended for induction therapy of cryptococcal meningitis.[66–68] There is also some evidence supporting the use of the combination of flucytosine and amphotericin B in meningitis caused by *Candida* species, *Penicillium marneffei*, and dematiacious molds.[61,69–73] The combination should be used with care because of the increased risk of toxicity with the combination. Flucytosine is eliminated primarily via the kidneys, so any nephrotoxicity caused by amphotericin will result in accumulation of flucytosine and an increase in its toxicity. The most common adverse effects are bone marrow suppression and hepatotoxicity.[61]

The azole class of medications is made up of two groups: the older imidazoles and the newer triazoles. The triazoles are generally considered more effective and better tolerated than the imidazoles in treating CNS fungal infections. Of the triazoles, fluconazole, itraconazole, and voriconazole have been sufficiently studied in fungal meningitis to be used as primary or secondary treatment. These medications play an important role in the treatment of *Coccidioides immitis, Aspergillus* species, hyaline molds, *Blastomyces dermatitidis, Candida* species, *Penicillium marneffei*, dematiacious molds, and *Cryptococcus neoformans*. Although amphotericin B in combination with flucytosine is still the recommended initial therapy for cryptococcal meningitis, fluconazole plays an important role in maintenance therapy.[60,61,66] Fluconazole is also useful in the treatment and prevention of *Coccidioides immitis* meningitis.[74] Voriconazole appears to be as effective as or more effective than amphotericin B in the treatment of invasive *Aspergillus* disease[75,76] and also has activity against *Fusarium* species, *Scedosporium* species, and dematiacious molds.[77,78] Itraconazole has limited CSF penetration,[79] and is less effective than fluconazole in treating cryptococcal infections.[60] However, itraconazole is a viable option in treating patients who are intolerant of fluconazole. Despite the promising data supporting the use of the triazoles, there are limited data directly comparing the triazoles to amphotericin B in the treatment of fungal meningitis. A recent Cochrane review attempted to compare the benefit and adverse effects of voriconazole versus amphotericin B in treating invasive fungal infections in neutropenic cancer patients. It only identified two studies that met the inclusion criteria and both studies were deemed flawed by the authors of the review. With the available data, the authors felt that amphotericin B was superior to voriconazole in treating all invasive fungal infections except aspergillosis, which was insufficiently studied.[80]

Caspofungin has significant fungal activity against *Candida* and *Aspergillus* species and is equal to amphotericin B or the azoles in treating infections caused by these organisms.[60,61] However, available data indicate that CNS penetration is low and there are no data on the use of capsofungin in CNS infections.[61] Micafungin and anidulafungin are among the other echinocandins being developed for treatment of fungal infections.[60] To date, none of the echinocandins has been studied in CNS fungal infections.

Specific Fungal Infections

A summary of the recommended therapies for fungal meningitis is presented in Table 16–5. The recommended initial treatment for cryptococcal meningitis, in both immunocompetent and immunosuppressed individuals, is a combination of amphotericin B (either 0.7 to 1 mg/kg daily IV of deoxycholate or 3–6 mg/kg daily IV of lipid formulations) and flucytosine (100 mg/ kg/day IV in four divided doses) for two weeks or until CSF cultures are negative.[60,66,68,81–83] Flucytosine blood levels should be obtained approximately 30 to 60 minutes after a dose. The goal is a level of 40–60 μg/mL. In patients that have renal failure or other complications limiting the use of amphotericin B, fluconazole 400 to 800 mg daily orally plus flucytosine is an appropriate alternative.[61,84,85] Amphotericin B lipid complex 5 mg/kg/day and Ambisome 4–6 mg/kg/day both have better CNS penetration and less nephrotoxicity and can be substituted for amphotericin B. Either amphotericin B or fluconazole can be used alone in the induction phase only in patients that cannot receive flucytosine.[84,86] After the initial two week induction, therapy should continue with either 10 weeks of fluconazole 400 mg daily orally or 6 to 10 weeks of amphotericin B in the same doses outlined above.[61] In patients with AIDS or other immunocompromised states, maintenance therapy is continued indefinitely while the patient remains immunocompromised. Fluconazole 200 mg daily orally is the ideal medication for maintenance therapy because it is well-tolerated and better than other medications in preventing relapses. Amphotericin B 0.6 to 1 mg/kg one to three times weekly IV and itraconazole 200 mg/day orally are alternatives in patients that cannot take fluconazole[67]>[87](Table 16–5).

Table 16–5 Treatment of Fungal Meningitis (Recommendations are in Bold)

Pathogen	Antifungal*
Cryptococcus neoformans (induction)	**Amphotericin B plus flucytosine for two weeks, followed by fluconazole for 10 weeks** or Amphotericin B plus flucytosine for two weeks, followed by amphotericin B for 6–10 weeks or Fluconazole plus flucytosine for two weeks, followed by fluconazole for 10 weeks
Cryptococcus neoformans (maintenance)	**Fluconazole** or Amphotericin B or Itraconazole
Coccidioides immitis (induction)	**Fluconazole** or Amphotericin B (intravenous plus intrathecal)
Coccidioides immitis (maintenance)	**Fluconazole** or Voriconazole or Posaconazole
Histoplasma capsulatum	**Amphotericin B**
Blastomyces dermatitidis	**Amphotericin B** or Fluconazole or Voriconazole
Candida spp.	**Amphotericin B plus flucytosine** or Fluconazole plus flucytosine
Aspergillus spp.	**Amphotericin B plus surgical resection** or Voriconazole plus surgical resection
Sporothrix schenckii	**Amphotericin B**
Penicillium marneffei	**Amphotericin B plus flucytosine** or Voriconazole
Dematiacious molds	**Surgical resection plus Amphotericin B plus flucytosine plus voriconazole**
Hyaline molds	Amphotericin B or Voriconazole
Zygomycetes	**Surgical resection plus Amphotericin B**

* Abelcet or Ambisome can be substituted for amphotericin B for the treatment of any of these fungi or molds.

Hydrocephalus with increased intracranial pressure (ICP) is an expected complication of fungal meningitis. The management of increased ICP is critical to successful outcome from cryptococcal meningitis. Intracranial pressure should be measured at the initial lumbar puncture, at the completion of induction therapy, and anytime during the course of the illness when the patient has a change in mental status or a change in the neurological examination (gait abnormalities, pathologically brisk reflexes, cranial nerve abnormalities, visual changes). The increased ICP is due to altered CSF hemodynamics and should be managed with daily lumbar punctures (to decrease CSF pressure by 50% and maintain CSF pressure at less than 300 mm H_2O), a ventriculostomy, or a ventriculoperitoneal shunt.

Meningitis due to *Coccidioides immitis* is also treated with an induction phase and maintenance phase. Fluconazole 400 to 800 mg/day orally is one of the recommended treatments for the induction phase. Some experts recommend a combination of intravenous amphotericin B (0.5 to 0.75 mg/kg/day) plus intrathecal amphotericin B instead of high dose fluconazole for induction therapy.[74] The duration of the induction phase is variable and based on clinical improvement. Since CNS infection with *C. immitis* is rarely cured, maintenance therapy with fluconazole 200 to 400 mg is recommended for lifelong prophylaxis.[88] If amphotericin B is used for the induction phase, the recommendation is that it be continued for at least a year after obtaining a normal CSF. Amphotericin B (0.5–0.75 mg/kg/day) plus intrathecal amphotericin B (0.25–0.75 mg/day three times weekly) or voriconazole (4 mg/kg every 12 hours orally) is recommended for induction therapy if fluconazole fails to provide clinical improvement.[74] Voriconazole and posaconazole also have excellent activity against *C. immitis* and might be useful in the treatment of *C. immitis* meningitis, but they have not been studied sufficiently to be recommended as routine therapy.

Although treatment of *Candida* infections has been studied extensively, there are limited data on the treatment of *Candida* meningitis due to its relative rarity.[61,89] Several small case series report successful treatment of *Candida* meningitis with amphotericin B alone (deoxycholate and liposomal formulations), the combination of amphotericin B and flucytosine, and the combination of fluconazole and flucytosine.[71,90–92] However, no studies have compared treatment options in *Candida* meningitis and dosing is not well-

defined. Recommended doses are the same as in cryptococcal meningitis. Due to the high tendency to relapse, therapy should continue for six to eight weeks or for four weeks after symptoms have resolved.[61,89] In patients with CNS devices and *Candida* meningitis, the device should be removed to obtain a complete cure.[93–94]

Infections due to other fungi, including ***Histoplasma capsulatum, Blastomyces dermatitidis, Aspergillus*** *species*, ***Sporothrix schenckii, Penicillium marneffei***, Zygomycetes, hyaline molds, and dematiacious molds can all be treated with Amphotericin B with or without flucytosine as outlined in Table 16–5. In CNS infections due to *Aspergillus, Penicillium marneffei, Blastomyces dermatitidis*, hyaline molds, and dematiacious molds, there are data to support the use of the triazoles, especially voriconazole. Appropriate dosing and duration of therapy are the same as in other forms of fungal meningitis. In addition, surgical resection of the lesions is recommended in infections due to *Aspergillus* species, dematiacious molds, and Zygomycetes.[61]

Herpes encephalitis

Herpes Simplex Virus-1

Empirical treatment should be initiated in all suspected cases of herpes simplex encephalitis (HSE) as shown in Figure **16–1**. Herpes simplex virus (HSV) encephalitis is treated with intravenous acyclovir at a dose of 10 mg/kg every eight hours.[95,96] The length of acyclovir treatment depends on multiple factors. If therapy is initiated because of suspected HSE, but an alternative diagnosis is made, acyclovir should be stopped. If the initial HSV PCR is negative, but the diagnosis of HSE is highly suspected, additional CSF should be obtained for PCR testing 72 hours after symptom onset and CSF for HSV antibodies should be obtained seven days after symptom onset. If HSV PCR is persistently negative, but the MRI demonstrates a lesion of increased signal intensity on T2-weighted and/or FLAIR imaging, the patient should be treated with 21 days of intravenous acyclovir or treated with acyclovir until an alternative diagnosis is made. When HSE is confirmed through PCR or HSV antibodies in the CSF, the patient should receive 21 days of intravenous acyclovir. Though initial studies treated patients for 10 days, one study showed 20% of patients had a positive PCR result after 14 days of treatment.[97] No formal studies have compared 10 days to 14 days to 21 days of acyclovir therapy. One study treated patients with a median of 14 days of acyclovir and reported 3 of 36 patients (8%) required a second course of acyclovir for a clinically suspected relapse.[98] Another study reported two relapses out of 53 (4%) when the length of acyclovir therapy was 10 days.[95] Based on limited data and the relative safety of acyclovir, all patients should receive 21 days of acyclovir if the diagnosis of HSE is confirmed or strongly suspected.

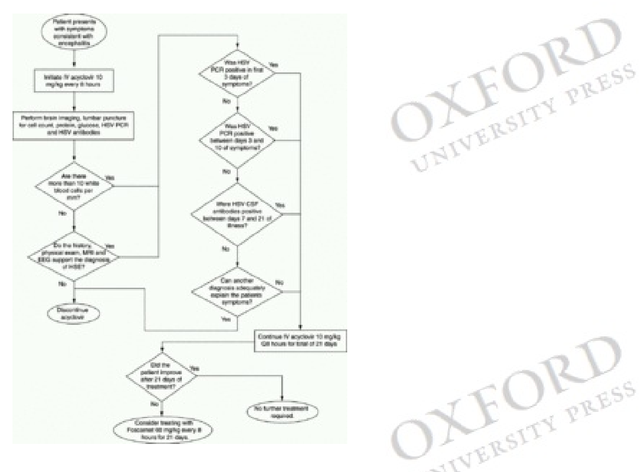




Figure 16—1.
An algorithm for the management of the patient with suspected HSV encephalitis.

Steroids have been studied as an adjunctive treatment in HSE. Two small case series showed reduced morbidity in patients treated with intravenous steroids at the onset of symptoms.[99,100] Future studies may confirm a benefit of steroid therapy, but currently there is not sufficient evidence to recommend corticosteroid therapy for HSE. Other therapies, including the use of interferons to prevent HSV-mediated neuronal death have been investigated in mice, but not in humans.[101,102]

In 5% to 30% of immunocompromised patients, acyclovir-resistant herpes simplex viruses have been isolated. Acyclovir is a purine nucleoside analog that is activated by herpes virus thymidine kinase. The activated acyclovir inhibits herpes DNA polymerase and prevents replication. Mutations in the viral genes encoding for thymidine kinase or DNA polymerase render acyclovir useless. Other thymidine kinase-dependent medications such as valacyclovir, penciclovir and famciclovir are also useless in treating resistant herpesviruses.[103] Foscarnet inhibits herpes DNA polymerase independent of thymidine kinase function. Dosed at 60 mg/ kg every eight hours for 21 days, it is effective in treating the majority of acyclovir-resistant herpesviruses, which have a thymidine kinase mutation.[103,104] However, some acyclovir-resistant herpesviruses, which develop resistance based on mutations in DNA polymerase, are also resistant to foscarnet.[105] Several articles report successful treatment of mucocutaneous HSV infections with cidofovir.[106–109] One study reported that all acyclovir-resistant, foscarnetresistant strains isolated in vitro were sensitive to cidofovir.[110] However, a recent case series reported three patients with cutaneous HSV infections that were unresponsive to cidofovir. One of the three HSV isolates demonstrated in vitro resistance to cidofovir.[111] There is no standard dose for the treatment of herpes simplex encephalitis with cidofovir.

Varicella-Zoster Virus

No randomized, controlled trials have compared the efficacy of acyclovir to any other viral agent in treatment of VZV encephalitis. Traditionally acyclovir has been used because of its relative safety and proven efficacy against HSV. The genetic similarity between VZV and HSV thymidine kinase suggests that therapies against HSV would also be effective against VZV.[112] Treatment with acyclovir 10 mg/kg IV three times per day for 14 to 21 days is recommended. Additionally, the use of steroids has been recommended to treat the inflammation associated with small or large-vessel vasculitis.[113] The addition of high-dose intravenous corticosteroids should be considered in patients that do not have a contraindication to the use of steroids.

Cytomegalovirus

Ganciclovir has been the mainstay of treatment for all CMV-related diseases since its approval in 1988.[114] The recommended dose of intravenous ganciclovir for CMV encephalitis is 5 mg/ kg IV every 12 hours for two weeks followed by maintenance therapy of 5 mg/kg/day IV.[115,116] Recently, oral valganciclovir became available, offering 10 times the bioavailability of oral ganciclovir[117] and similar bioavailability to intravenous ganciclovir.[118,119] No studies report a benefit of oral valganciclovir over intravenous ganciclovir in CMV encephalitis. Cidofovir and foscarnet are also used in the treatment of CMV encephalitis.[114] The recommended dose of foscarnet for CMV encephalitis or retinitis is 180 mg/kg/day (either 60 mg/kg every eight hours or 90 mg/kg every 12 hours) intravenously for two weeks followed by 60–120 mg/kg daily.[120,121] The use of foscarnet as an adjunct to ganciclovir in CMV encephalitis has been advocated,[115,116] and is supported by one in vitro study[122] and one in vivo study treating CMV retinitis.[121] The major limitation of the combination therapy is toxicity. However, a study comparing full dose ganciclovir to half-dose ganciclovir plus half-dose foscarnet showed no superiority of combination therapy.[123]

The optimal duration of therapy for any of the anti-CMV medications remains unclear. None of the agents completely eradicates the infection, so maintenance therapy is often required long-term for viral suppression. If a patient had CMV encephalitis while in a temporary immunocompromised state and there is reconstitution of the immune system, maintenance therapy could be stopped. However, the majority of patients with CMV encephalitis have an underlying chronic immunodeficiency that may require lifelong anti-CMV therapy to prevent recurrences. Our recommendation is to treat with two weeks of full dose ganciclovir (5 mg/ kg every 12 hours IV) followed by maintenance therapy (5 mg/kg daily IV). Patients that relapse, or fail to improve after two weeks, should receive full-dose foscarnet therapy for two weeks (60 mg/kg every eight hours IV) followed by foscarnet maintenance therapy (60–120 mg/kg daily IV) indefinitely. Alternative regimens include the combination of ganciclovir and foscarnet (in full doses as outlined above) or cidofovir. If the combination of ganciclovir and foscarnet causes significant adverse effects, one of the agents can be stopped and the other continued. Another option is to use cidofovir 5 mg/kg weekly IV for two weeks, then 5 mg/kg every two weeks IV for maintenance. Patients should be pretreated with probenecid 2g orally three hours before the cidofovir, then an additional 1g two and eight hours after the cidofovir.

Human Herpesvirus (HHV) Type 6 and 7

Although no clinical trials have established the efficacy of any one antiviral agent in the treatment of HHV-6 encephalitis, some small series indicate successful treatment with either ganciclovir or foscarnet.[124–127] The course of treatment with ganciclovir or foscarnet has not been established, but because the in vitro response to antiviral medications resembles that of CMV, treatment of HHV-6 encephalitis should be the same as the treatment for CMV encephalitis.[128] Treatment with donor leukocyte infusion has been described, but remains an unproven therapy.[124] Because of the similarity of HHV-7 with HHV-6, treatment of HHV-7 encephalitis should be the same as treatment of HHV-6 encephalitis.

Epstein-Barr Virus

No therapy has proven to decrease morbidity associated with Epstein-Barr virus (EBV) encephalitis. Although studies do show decreased shedding of virus with acyclovir therapy, there is no statistically significant benefit to acyclovir therapy in infectious mononucleosis.[129] There are anecdotal reports of the benefit of acyclovir and ganciclovir in the treatment of EBV encephalitis, but definitive treatment has not been established by clinical trials. Corticosteroids have been shown to improve EBV-related acute disseminated encephalomyelitis, but not EBV encephalitis.[130] Because of the generally favorable outcomes in EBV encephalitis, no specific antiviral or immunomodulating therapies are recommended.

Toxoplasmosis encephalitis

Toxoplasmosis encephalitis is treated with an induction phase to eliminate active tachyzoites, and chronic suppressive therapy to prevent reactivation from tissue cysts.[131,132] The recommended induction phase medications are pyrimethamine 100–120 mg oral loading dose, then 50 to 100 mg/day orally and sulfadiazine 1–1.5g every six hours orally. Both of these medications block folate metabolism, so folinic acid (leucovorin) 10 to 25 mg/day orally s added to reduce toxicity.[131,133–137] The induction phase should continue for six weeks, although a shorter regimen is acceptable in patients with a rapid response or clear resolution of lesions.[84] The main limitation of the pyrimethamine and sulfadiazine combination is toxicity, occurring in more than half of patients.[131,133,135] Several other medications have activity against *Toxoplasma gondii* and might provide a less-toxic alternative to the pyrimethamine and sulfadiazine combination.[132,138–140] The main alternative is the combination of pyrimethamine and clindamycin, which appears to have a similar initial response rate to the pyrimethamine and sulfadiazine combination with less toxicity (see Table 16–6).[133,135,136,140] Relapse rates are very high when treatment is stopped after the induction phase.[131,139,141]

Table 16–6 Treatment of *Toxoplasma Gondii*

Induction	**Pyrimethamine plus sulfadiazine plus folinic acid for six weeks** or Pyrimethamine plus clindamycin plus folinic acid for six weeks or Pyrimethamine plus clarithromycin plus folinic acid for six weeks or Pyrimethamine plus azithromycin plus folinic acid for six weeks or Pyrimethamine plus dapsone plus folinic acid for six weeks or Pyrimethamine plus atovaquone plus folinic acid for six weeks or Sulfadiazine plus atovaquone for six weeks
Maintenance	**Pyrimethamine plus sulfadiazine plus folinic acid** or Pyrimethamine plus clindamycin plus folinic acid or Atovaquone or Pyrimethamine plus atovaquone plus folinic acid

Therefore, suppressive therapy should continue as long as the patient has an impaired immune response. Choices of medications for chronic suppressive therapy are as follows: pyrimethamine 25–50 mg daily plus either sulfadizine 1 g thrice daily orally or clindamycin 300 mg thrice daily orally. The use of corticosteroids in toxoplasmosis encephalitis is controversial and although there is no definite contraindication, they should not be used routinely.[137,142] In patients that are severely immunocompromised (CD4 counts below 100 cells/pL), primary prophylaxis is indicated. The recommended prophylactic medication choice is trimethoprim-sulfamethoxazole 160/800 mg daily orally and should continue until CD4 counts are greater than 200 cells/pL for at least three months[137,139,141] (Table 16–6).

Progressive multifocal leukoencephalopathy

The primary goal in the treatment of progressive multifocal leukoencephalopathy (PML) is reconstitution of the immune system. Progressive multifocal leukoencephalopathy occurs primarily in severely immunocompromised patients with CD4 counts below 100 cells/μL, but also occurs in AIDS patients with somewhat higher CD4 counts.[84,132,137,143–145] Highly active antiretroviral therapy (HAART) prolongs survival and increased CD4 counts improve outcomes in AIDS patients with PML.[84] Reversing immunosuppression also appears to be beneficial in non-AIDS patients with PML.[146] A recent case report describes complete resolution of PML lesions after stopping immunosuppression in a renal transplant patient.[147] Regardless of the etiology of the patient's immunosuppressed state, reconstitution of the immune system should be the first course of treatment. The role of antiviral medications directed at the JC virus is unclear. Cytosine arabinoside, amantadine, vidarabine, acyclovir, and interferon alpha have all been used without success in treating PML.[134,137,143,148] Cidofovir has good in vitro activity against polyoma viruses related to JC virus.[149] A retrospective study showed a benefit to the use of cidofovir in patients on HAART,[150] but several prospective studies demonstrated no benefit of cidofovir plus HAART over HAART alone.[144,145,151] Based on

these studies and the relatively high risk of serious side effects from cidofovir, there is insufficient evidence to recommend routine use of cidofovir in PML. A recent case report describes remission of PML in an AIDS patient treated with combination of cidofovir and radiation designed to break down the blood brain barrier (BBB) and allow higher penetration of cidofovir.[152]

Hiv neuropathy, myelopathy, encephalitis

There are currently no therapies proven to modify the course of HIV-related neuropathy or myelopathy. The incidence of neuropathy and myelopathy have decreased with the use of HAART, and progression of these diseases might slow with HAART.[153–155] However, the mainstay of treatment is symptomatic therapy. HIV-related neuropathy is treated similarly to painful diabetic polyneuropathy with tricyclic antidepressants, anticonvulsants, opioids, and the lidocaine patch. Symptomatic treatment of HIV-associated myelopathy is the same as treatment of any form of myelopathy. Benzodiazepines and baclofen can reduce spasticity and anticholinergic or cholinergic medications are used for spastic or flaccid bladder. In HIV-dementia, HAART does appear to improve cognitive function.[153] Many drugs have been studied in an attempt to provide neuroprotection in HIV-dementia, but none has shown a convincing benefit to warrant routine usage.[156]

Tuberculous meningitis

Due to the low toxicity of antituberculous medications in short-term use, empirical therapy should be initiated early in patients with a reasonable suspicion for tuberculous meningitis to reduce morbidity and mortality.[157,158] A reasonable suspicion is defined by the presence of fever and headache associated with a CSF lymphocytic pleocytosis and a mildly decreased glucose concentration (25–40 mg/ dL). Five medications—isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin— are considered first-line therapies. Initial therapy in suspected tuberculous meningitis consists of three of the first-line medications.[159–161] Isoniazid and pyrazinamide easily penetrate inflamed or uninflamed meninges[161] and, unless there is a contraindication to their use, they should always be used in the initial treatment of tuberculous meningitis. The most common initial regimen is isoniazid, rifampin, and pyrazinamide dosed according to Table 16–7.[159,162] In areas where local resistance is unknown or greater than 4%, a fourth drug (either ethambutol or streptomycin) is added. If tuberculous meningitis is confirmed, the initial therapy is continued for two months, followed by isoniazid and rifampin daily or twice weekly for four months.[159,160] After confirmation, susceptibility testing should be performed and if there is resistance to any of the drugs, another should be used in its place. There are case reports of multidrug resistant tuberculous meningitis,[163–168] but this currently appears to be a minor threat at the present time. In these cases, therapy is tailored based on the susceptibility testing.[159,169] If there is a slow clinical response to medications or if CSF cultures remain positive for prolonged periods of time, therapy should continue for 12 to 18 months, or for six months after cultures become negative[170] (Table 16–7).

Table 16–7 Treatment of Tuberculous Meningitis

Medication	Dosing
Ethambutol	15–25 mg/kg daily
Isoniazid (pediatric)	10 mg/kg daily orally or IM
Isoniazid (adult)	300 mg daily orally or IM
Pyrazinamide (pediatric)	20–30 mg/kg daily orally
Pyrazinamide (adult)	20–35 mg/kg daily orally
Rifampin (pediatric)	10–20 mg/kg daily orally or IV
Rifampin (adult)	600–1200 mg/day (300–600 mg every 12 hours) orally or IV
Streptomycin (pediatric)	20–30 mg/kg daily IM
Streptomycin (adult)	15 mg/kg daily IM



Liver enzymes should be monitored periodically throughout the treatment period.Although the medications are usually well-tolerated, significant elevations in aminotransferases (>5 times normal) require replacing isoniazid and rifampin with ethambutol and streptomycin. When the liver enzymes return to normal, treatment can revert back to isoniazid and rifampin, but biweekly liver enzymes should be monitored. In preganancy, isoniazid and ethambutol are considered safe, rifampin is relatively contraindicated, streptomycin has been associated with a risk of congenital deafness and there is a lack of data on pyrazinamide.[162]

The role of steroids as an adjunctive therapy in tuberculous meningitis has been debated for many years. Several small case series showed a potential benefit of using steroids in treating tuberculous meningitis, but the clinical significance of the limited data is unclear.[158,171–173] A recent prospective, doubleblind, placebo-controlled trial demonstrated a benefit in patients treated with dexamethasone regardless of HIV status. Mortality was reduced significantly in the treatment group, and though there were fewer overall adverse effects, morbidity of survivors was not affected by treatment. Patients with a Glasgow Coma Scale score of 15 and no focal neurological deficits received intravenous dexamethasone 0.3 mg/kg daily for one week and 0.2 mg/kg daily for one week followed by four weeks of oral therapy (0.1 mg/kg daily for one week, then a tapering dose of 3 mg daily for one week, 2 mg daily for one week, and 1 mg daily for one week). All other patients received intravenous treatment for four weeks (0.4 mg/kg daily for week one, 0.3 mg/kg daily for week two, 0.2 mg/kg daily for week three, and 0.1 mg/kg daily for week four) followed by an oral taper for four weeks, starting at a total of 4 mg daily and decreasing by 1 mg each week.[174]

There is general agreement that dexametha sone therapy should be used for patients with altered consciousness, papilledema, focal neurological signs, impending herniation, spinal block, and hydrocephalus. In addition, as patients are treated for tuberculous meningitis, the slow resolution of the inflammatory exudate in the basilar cisterns may obstruct the flow and resorption of CSF with the subsequent development of hydrocephalus. These patients may need either a short course of oral steroid therapy or a ventriculoperitoneal shunt.

Neurosyphilis

It is recommended that patients be treated for neurosyphilis when they have a positive serological test (VDRL or FTA-ABS) and a CSF lymphocytic pleocytosis with an elevated protein concentration whether the CSF VDRL is reactive or not. Any patient with a reactive CSF VDRL should be treated for neurosyphilis. The treatment of choice for neurosyphilis is intravenous aqueous crystalline penicillin G 3–4 million units every four hours for 10–14 days. Aqueous penicillin G is given every four hours to achieve consistent treponemicidal concentrations in CSF. An alternate regimen is procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg orally four times a day for 10–14 days.[175] For patients who are allergic to penicillin, an effort should be made initially to desensitize these patients. Either regimen is followed by 2.4 million units of benzathine penicillin G intramuscularly once a week for three weeks. Neurosyphilis has been treated successfully in patients that are HIV-infected with ceftriaxone (2

gm intravenously once daily for 10–14 days), and minocycline has been studied in HIV negative patients with neurosyphilis.[176,177]

In patients who have been treated for neurosyphilis, the CSF should be reexamined at six monthly intervals for two years. The initial CSF pleocytosis will resolve six months after penicillin therapy in 80% of patients. Serial CSF VDRL titers should decrease by two dilutions or revert to nonreactive within two years of the completion of therapy. An increase in the CSF VDRL titer by two or more dilutions or a failure of the CSF pleocytosis to resolve within 12 months suggests either persistent infection or reinfection, and requires retreatment.

Lyme disease

Lyme disease meningitis, cranial neuritis and radiculitis is treated with ceftriaxone 2 g once per day intravenously for 21 days. Doxycycline 200–400 mg per day in two divided doses orally for 10–14 days has been used successfully in Europe for the treatment of meningitis due to Lyme disease in adults and in children >8 years of age.[178]

Neurocysticercosis

There is controversy about whether anticysticidal drug therapy modifies the course of neurocysticercosis. There is universal agreement that treatment is not indicated for calcified lesions.

Cysticidal drug therapy, either albendazole (15 mg/kg/day for four weeks) or praziquantel (50 mg/kg/day for two to three weeks), is recommended for viable and degenerating parenchymal cysts. Degenerating cysts cause a granulomatous inflammatory response by the host and appear as enhancing lesions often associated with edema. Corticosteroid therapy should be used prior to and concomitant with cysticidal drugs to reduce the edema associated with cysticidal drug therapy. Seizures should be treated with anticonvulsants. There is controversy whether or not a solid nodular lesion, which represents a more advanced stage of degeneration, should be treated with antihelminthic therapy.

Conclusion

Table 16–8 provides a list of the doses of antimicrobial agents for the treatment of CNS infections. Doses and choices of antimicrobial agents may need to be modified based on the response of the patient. Kidney and liver function as well as CBC should be monitored throughout therapy. As a general rule, the clinical response of the patient and the CSF culture results are critical to duration of therapy (Table 16–8).

Table 16–8 Dosing of Antimicrobial Agents for Treatment of CNS Infections

Antimicrobial Agent	Dosing*
Acyclovir (pediatric)	60 mg/kg per day IV (20 mg/kg every eight hours)
Acyclovir (adult)	30 mg/kg per day IV (10 mg/kg every eight hours)
Albendazole	15 mg/kg daily orally
Amphotericin B (induction)	0.7–1 mg/kg daily IV
Amphotericin B (maintenance)	0.6–1 mg/kg IV one to three times per week
Abelcet	5 mg/kg daily IV
Ambisome	4–6 mg/kg/day
Intrathecal amphotericin	0.25–0.75 mg three times/week
Ampicillin (pediatric)	300–400 mg/kg per day (50–66 mg/kg every four hours)
Ampicillin (adult)	12–15 g/day (2–2.5 grams every four hours or 3–3.75 grams every six hours)
Amoxicillin	1500 mg/day (500 mg thrice daily) orally
Atovaquone (induction)	3 g/day orally (750 mg every six hours or 1500 mg every 12 hours)
Atovaquone (maintenance)	1.5–3 g/day orally (750 mg every 6–12 hours)
Azithromycin	1.2–1.5 g/day orally
Cefepime	4 g/day (2 g every 12 hours)
Cefotaxime (pediatric)	300 mg/kg per day (75 mg/kg every six hours)
Cefotaxime (adult)	12g/day (2 g every four hours) or half this dose for Lyme disease
Ceftazidime	6 g/day (2 g every eight hours)
Ceftriaxone (pediatric)	80–100 mg/kg per day (40–50 mg/kg every 12 hours)
Ceftriaxone (adult)	4 g/day (2 g every 12 hours) or half this dose for Lyme disease
Cefuroxime	1000 mg/day (500 mg twice daily) orally

Cidofovir (induction)	5 mg/kg weekly IV
Cidofovir (maintenance)	5 mg/kg every two weeks IV
Clarithromycin	2 g/day orally (1 g every 12 hours)
Clindamycin (induction)	2.4–3.6 g/day orally or IV (600–900 mg every six hours)
Clindamycin (maintenance)	900–1800 mg/day orally (300–450 mg every six to eight hours)
Dapsone	100 mg daily orally
Doxycycline	200 mg/day (100 mg every 12 hours)
Ethambutol	15–25 mg/kg daily
Fluconazole (induction)	400–800 mg daily orally
Fluconazole (maintenance)	200–400 mg daily orally
Flucytosine	100 mg/kg per day orally (25 mg/kg every six hours)
Folinic acid	10–25 mg daily orally
Foscarnet (induction)	180 mg/kg per day IV (60 mg/kg every eight hours or 90 mg/kg every 12 hours)
Foscarnet (maintenance)	90–120 mg/kg daily IV
Ganciclovir (induction)	10–12 mg/kg per day IV (5–6 mg/kg every 12 hours)
Ganciclovir (maintenance)	5–6 mg/kg daily IV for five to seven days per week
Gentamicin[l], tobramycin[l]	6 mg/kg per day (2 mg/kg every eight hours)
Itraconazole (induction)	400 mg daily orally
Itraconazole (maintenance)	200 mg daily orally
Isoniazid (pediatric)	10 mg/kg daily orally or IM
Meropenem	6 g/day (2 g every eight hours)
Metronidazole	2000 mg/day (500 mg every six hours)
Nafcillin (adult)	12 g/day (2 g every four hours or 3 g every six hours)
Oxacillin	12 g/day (2 g every four hours or 3 g every six hours)
Penicillin G	18–24 million units/day (3–4 million units every four hours) IV
Penicillin (procaine)	2.4 million units once daily IM
Pleconaril (infants)	15 mg/kg/day (5 mg/kg every eight hours) orally
Praziquantel	50 mg/kg daily orally or 25–33 mg/kg every two hours for three total doses
Probenecid	2 g/day (500 mg every six hours) orally
Pyrazinamide (pediatric)	20–30 mg/kg daily orally
Pyrazinamide (adult)	20–35 mg/kg daily orally
Pyrimethamine (induction)	100–120 mg loading dose, then 50–100 mg orally daily
Pyrimethamine (maintenance)	25–50 mg daily orally
Rifampin (pediatric)	10–20 mg/kg daily orally or IV
Rifampin (adult)	600–1200 mg/day (300–600 mg every 12 hours) orally or IV
Spiramycin	3 g daily orally

Streptomycin (pediatric)	20–30 mg/kg daily IM
Streptomycin (adult)	15 mg/kg daily IM
Sulfadiazine (induction)	4–6 g/day orally (1–1.5 g every six hours)
Sulfadiazine (maintenance)	2–4 g/day orally (0.5–1 gram every six hours)
Trimethoprim-sulfamethoxazole	15–20 mg/kg per day of TMP component orally or IV (5–6.67 mg/ kg every eight hours)
Valacyclovir	2 g/day orally (1000 mg twice daily)
Vancomycin[1]	40–60 mg/kg per day IV (every six hour or 12 hour dosing intervals)
Vancomycin (intrathecal)	Pediatric dose: 10 mg/day Adult dose: 20 mg/day
Voriconazole	8 mg/kg per day (4 mg/kg every 12 hours) orally

* Reduction of dose of the antibiotics (with the exception of ceftriaxone) in case of renal failure is necessary.

[1] Determination of the serum concentrations are required; recommended peak levels one hour after intravenous administration: gentamicin and tobramycin 5–10 µg/mL; vancomycin 25 µg/mL.

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Therapies for the Neurological Complications of HIV Infection

Chapter: Therapies for the Neurological Complications of HIV Infection
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Neurons are rarely infected by the human immunodeficiency virus (HIV), yet neuronal loss in patients with HIV infection is common, likely due to the effects of viral proteins and inflammatory mediators on these cells. HIV infection thereby frequently causes cognitive impairment and other neurological complications, often striking patients during the prime working years of their lives, with major personal and socioeconomic consequences. Highly active antiretroviral therapy (HAART) has reduced the incidence of severe forms of HIV associated dementia, but milder forms persist. Highly active antiretroviral therapy has also allowed patients to live longer with HIV infection, and the prevalence of HIV dementia is actually rising.[1–5] Additionally, many patients are noncompliant with complicated HAART regimens or their HIV infection may become resistant to available HAART therapies. Some patients, especially in developing nations, may not have access to these drugs. Fortunately, important recent findings have advanced our understanding of the molecular mechanisms by which HIV infection causes neuronal damage, demonstrating numerous potential therapeutic targets.[6]

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HIV-Associated dementia

Up to 500 000 people in the United States alone are affected by HIV-induced brain injury,[7] which can vary in severity from mild cognitive impairment to dementia. Although HIV-associated dementia (HIVD) classically affects patients with advanced immunosuppression, it can occur even as the presenting symptom of HIV infection.[8–10] Unlike the more traditional cortical dementias marked by memory loss, HIVD is termed a subcortical dementia and typically affects a triad of neurological domains—cognitive, motor, and behavioral. The cognitive manifestations are marked by psychomotor retardation and forgetfulness. The motor effects present in a variety of ways including tremors, incoordination, parkinsonism, and impaired balance.[11] The behavioral impairments usually occur as a general apathy, social withdrawal, depression, psychosis, or emotional incontinence.

Host susceptibility and viral virulence factors play a key role in determining which patients develop dementia.[12] HIV enters the brain within days to weeks of initial infection, but is usually controlled rapidly. It may be years before patients develop any dementing signs or symptoms, or they may never develop dementia at all.[13–15] When HIV dementia occurs, it is probably the result of an inflammatory cascade that HAART fails to target. Significant research is focused on the mechanisms underlying these events, because understanding this pathogenesis should ultimately allow development of immunomodulatory therapies for treating HIV infection, other viral encephalitides, and perhaps other neuroinflammatory conditions as well.

Other hiv-related neurological disease

In addition to HIV dementia, HIV infection causes or contributes to numerous other neurological conditions, most commonly vacuolar myelopathy and peripheral neuropathy. HIV vacuolar myelopathy, as its name implies, is a form of spinal cord injury caused by HIV,[16] presenting with progressive bladder dysfunction and spasticity, weakness, and loss of sensation, especially in the legs.[17] There is edema in the myelin with relative sparing of axons, and some evidence suggests a pathogenic role in this condition for macrophages and cytokines.[18,19]

Peripheral neuropathy is probably the most common neurological complication of HIV infection.[20] Symptoms occur in the distal extremities, particularly the feet, and include predominantly pain, but also numbness, paresthesias, and autonomic dysfunction. As with HIV dementia and vacuolar myelopathy, the host reponse has been implicated in the pathogenesis of this HIV-related complication as well.[21] Antiretroviral-induced toxic neuropathies present with similar symptoms, but are likely due to interference with DNA synthesis and mitochondrial dysfunction.[21] There may be a synergism between the neurotoxicity of HIV infection and the neurotoxicity of the drugs in producing peripheral neuropathies.

Though the neurological complications of HIV infection are numerous, most studies have focused on the pathogenic mechanisms of HIV dementia. Although the details may vary, it is likely that the basic mechanisms of HIV neuropathogenesis will be similar across these clinical entities, and perhaps even in other neuroinfectious and neuroinflammatory conditions. Figure **17–1** depicts the basic molecular mechanisms involved in HIV neuropathogenesis.

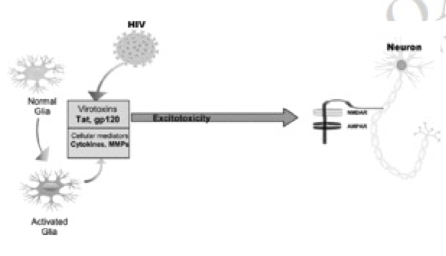


Figure 17—1.
Cascade of events in the neuropathogenesis of HIV dementia.

Pathology

Activated Macrophages and Microglia

Pathologically, HIV dementia is marked by activated macrophages in the white matter,[22] multinucleated giant cells representing virally induced fusion of macrophages,[23] microglial nodules, and perivascular mononuclear inflammation.[24,25] HIV-1 infection or viral proteins, such as gp120 and Tat, can activate uninfected cells.[26,27] Although these cells may have some neuroprotective properties, especially early in the infection,[28,29] their main role in HIV dementia seems to be neuroinflammatory due to their expression of various neurotoxic factors, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interferon-α (INF-α), and nitric oxide synthase (NOS).[30,31]

Astrocytes

Astrocytes will develop a restricted HIV infection in which viral proteins are expressed, but replication of the viral genome does not occur.[32] HIV-infected astrocytes are known to overexpress Tat, Nef, and Rev.[33,34] Restricted infection thus represents a major source of viral proteins that can damage neurons. Protease is not required for production of Tat, Nef, and Rev, and once the viral genome is integrated into the astrocyte genome, production of these proteins occurs without the use of reverse transcriptase. Thus, while HAART can clearly impact dementia by reducing viral replication and integration subsequent to HAART initiation, the reverse transcriptase inhibitors and protease inhibitors are unable to affect the production of proteins from the virus that is integrated prior to initiation of HAART. Substantial integration is likely to occur quickly after primary HIV infection, well before HAART is initiated. Reactive astrocytes are also likely to lose their normal ability for neuronal support functions, and are capable of expressing inflammatory mediators, including TNF-α.[35]

Loss of Neurons

Though neurons are rarely infected by HIV,[36] neuronal loss is common, likely due to viral proteins and inflammatory mediators. Magnetic resonance spectroscopy shows decreased N-acetyl aspartate, a neuronal marker, in the basal ganglia of patients with mild to moderate HIV dementia, suggesting that neuronal injury correlates with development of dementia.[37,38] Furthermore, the most common abnormality on brain imaging of patients with HIV dementia is subcortical cerebral atrophy, even when clinical deficits are still mild.[39–45] Cerebral atrophy, however, is also frequently seen in HIV-infected but nondemented patients,[43,44] and is not well correlated with dementia severity.[46] Several studies have demonstrated the presence of apoptotic neurons, as detected by terminal uridine deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) positive cells, DNA laddering, and electron microscopic changes, at autopsy in HIV infected patients. Neuronal apoptosis is more severe in atrophic brains[47] and correlates with microglial activation,[48] suggesting that the inflammatory mediators secreted by microglia play an important role in initiating apoptotic cascades. However, neuronal apoptosis seems to be a late event, and HIV dementia more likely reflects various mechanisms of neuronal dysfunction. Some forms of neuronal dysfunction, such as morphological changes in dendrites and loss of neurites without neuronal cell loss[49] may be reversible,[50] if adequate treatments can be developed.

Differential Effects on Specific Brain Regions and Neuronal Populations

Basal ganglia and hippocampus are preferentially affected in HIV dementia, with neuronal losses of up to 50%–90%,[51–55] significant reduction in hippocampal dendritic arborization,[56] and impaired hippocampal synaptic function.[57] The frontal lobes have 40%–60% neuronal loss and the parietal and temporal lobes have approximately 20% loss,[49,58–60] while the cerebellum and occipital lobes are relatively spared. The predominance of changes in basal ganglia and hippocampus may account for many of the symptoms of HIV dementia, including psychomotor slowing and memory impairment.

Neurons that express non-N-methyl-Daspartate (NMDA) excitatory amino acid receptors appear preferentially targeted,[61,62] along with the dopaminergic system. Positron emission tomography (PET) studies demonstrate lower dopamine transporter availability in the basal ganglia of HIV-positive patients with dementia.[63] Simian immunodeficiency virus (SIV)-infected rhesus monkeys have decreased levels of dopamine, dopamine metabolites, and dopamine signaling, even during early, asymptomatic infection.[64] Damage to the dopaminergic system could explain the motor manifestations, particularly parkinsonism, frequently seen in patients with HIV dementia.

Detection of a particular pattern of regional metabolic change, for example, by magnetic resonance spectroscopy (MRS), may enable earlier diagnosis of dementia or even identification of asymptomatic individuals susceptible to dementia,[65–67] leading to the opportunity for earlier therapeutic intervention or monitoring of treatment efficacy.[66,68]

State of the Blood Brain Barrier

Impairment of either endothelial cell or astrocytic function can compromise the blood brain barrier (BBB). The viral Tat protein affects the expression and assembly of tight

junction proteins, leading to cytoskeletal disruption of endothelial cells and increased endothelial permeability.[69,70] Not only can HIV cross the BBB in infected immune cells, but cell-free HIV can transmigrate through as well.[71,72] The periventricular white matter of patients with HIV dementia is pale, not due to demyelination, but to these changes in the BBB.[73–75] White matter changes, especially when confluent, correlate with immune infiltration, extravasation of protein, and BBB compromise.[73] These white matter changes can sometimes be reversed by HAART, and that reversal is often associated with cognitive improvement.[76]

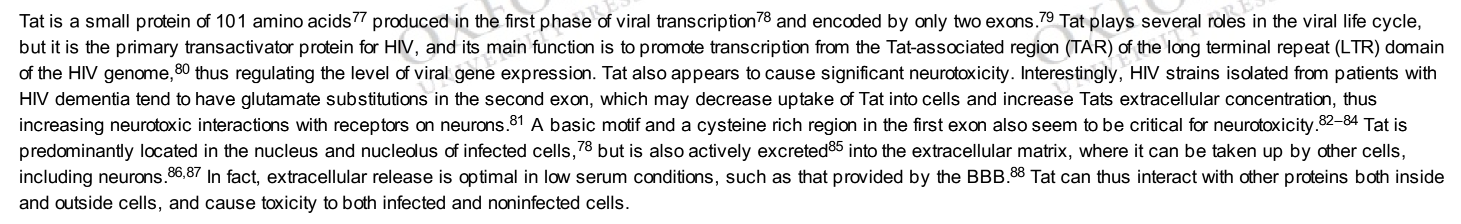
Role of viral proteins

Several viral proteins, including vpr, Nef, and Rev, are thought to contribute to the neuropathogenesis of HIV dementia, although the effects of only Tat and gp120 have been well characterized. Other HIV proteins, including p24, reverse transcriptase, protease, endonuclease, vpu, and vif, are either felt to be nontoxic, or their neurotoxic potential is unstudied and thus unknown. See Table 17–1 for a list of the implicated viral proteins.

Table 17–1 Viral Proteins and Host Factors Implicated in HIV Neuropathogenesis
Viral Proteins
gp120
Nef
Rev
Tat
vpr
Host Factors
Apolipoprotein E
Chemokines
Including CCR1, CCR3, CCR5, CXCR4, fractalkine, MCP-1, MIP-α, RANTES
Cyclooxygenase-2
Cytokines
Including IL-1β, IL-6, IL-8, TNF-α
Growth factors
Matrix metalloproteinases
Nitrosative stress
Oxidative stress



Tat



Tat is a small protein of 101 amino acids[77] produced in the first phase of viral transcription[78] and encoded by only two exons.[79] Tat plays several roles in the viral life cycle, but it is the primary transactivator protein for HIV, and its main function is to promote transcription from the Tat-associated region (TAR) of the long terminal repeat (LTR) domain of the HIV genome,[80] thus regulating the level of viral gene expression. Tat also appears to cause significant neurotoxicity. Interestingly, HIV strains isolated from patients with HIV dementia tend to have glutamate substitutions in the second exon, which may decrease uptake of Tat into cells and increase Tats extracellular concentration, thus increasing neurotoxic interactions with receptors on neurons.[81] A basic motif and a cysteine rich region in the first exon also seem to be critical for neurotoxicity.[82–84] Tat is predominantly located in the nucleus and nucleolus of infected cells,[78] but is also actively excreted[85] into the extracellular matrix, where it can be taken up by other cells, including neurons.[86,87] In fact, extracellular release is optimal in low serum conditions, such as that provided by the BBB.[88] Tat can thus interact with other proteins both inside and outside cells, and cause toxicity to both infected and noninfected cells.

The neurotoxicity of Tat (and other viral proteins) has been demonstrated primarily by in vitro studies using neuronal cultures and in vivo by intracerebral injection of recombinant protein into animals. The former technique obviously lacks the complexities of an in vivo system, while, in the latter, the stress and damage induced by the technique itself may contribute to the observed pathology. However, a transgenic mouse model has also been established in which Tat expression is doxycycline-inducible and is regulated by a glial fibrillary acidic protein promoter to ensure expression only in astrocytes. The behavioral and pathological features of these mice are very similar to those found in patients with HIV dementia, demonstrating that the presence of Tat protein, even in the absence of HIV infection, is sufficient to cause much of the neuropathogenesis associated with HIV.[89]

Numerous mechanisms have been implicated for Tat-induced neurotoxicity. One important mechanism is derangement of calcium homeostasis,[90] probably mediated by Tat activation of chemokine receptors, including CCR2, CCR3, and the receptors for MCP-1, MCP-3, and eotaxin.[91] Elevated intracellular calcium levels initiate a cascade of events including attenuation of mitochondrial membrane potential, increased free radical production, activation of caspases, and apoptosis.[92,93] Tat also causes excitotoxity by directly stimulating the neuronal glutamate NMDA receptor, perhaps through the polyamine region of the receptor.[94] An antagonist to the polyamine site attenuates Tats effects on intraneuronal calcium levels.[95] Tat also promotes the NMDA receptor's phosphorylation, leading to its further stimulation,[96] resulting in a long cascade with increased calcium, nitric oxide, and free radicals, producing oxidative damage, energy failure, and DNA damage.

Tat also stimulates monocytes, macrophages, and astrocytes to produce numerous inflammatory cytokines and chemokines,[97–99] including IL-1, IL-8, RANTES, TNF-a,93,i00-i02 SDF1,103 and MCP-1.104 TNF-α and SDF-1 mediate neurotoxicity,[102,105] and MCP-1 is a potent chemoattractant for monocytes.[106] Tat-induced leukocyte transmigration across an in vitro BBB model can be blocked by antisera to MCP-1.[98] Many of these cytokines/chemokines have both deleterious and beneficial effects[107,108] so the net effect is likely the result of a complex set of interactions and conditions, and is very difficult to predict a priori or to determine experimentally. Tat also causes neurotoxicity through increases in oxidative stress. Among other mechanisms, it downregulates manganese superoxide dismutase contributing to production of reactive oxygen species,[109] and increases expression of nitric oxide synthase in microglia and astrocytes.[110,111]

Gp120

The env gene of the HIV genome encodes gp160, which is cleaved to form the two major envelope proteins of HIV, gp41 and gp120. When HIV infects a cell, its envelope, including both gp120 and gp41, is either incorporated in the infected cell's membrane or shed into the extracellular milieu,[112] where they are available for direct toxic effects on neurons. Study of gp41 neurotoxicity has been limited. It induces nitric oxide synthase in glial cells,[113,114] reduces glutathione levels and mitochondrial function in neurons,[115] and promotes excitotoxicity by decreasing the uptake and stimulating the release of glutamate in astrocyte cultures.[116]

The neurotoxicity of gp120, on the other hand, has been extensively studied. Its neurotoxic effects are largely mediated through glial cells, but it can affect neurons directly.[117–120] Astrocytes normally are very efficient at absorbing glutamate, a characteristic felt to be important in preventing excitotoxicity that might be caused by glutamate accumulation.[121] Gp120 diminishes this protective function of astrocytes by stimulating a sodium-proton exchanger[122,123] and attenuating a sodium gradient.[124] Gp120 may also decrease glutamate uptake by downregulating the EAAT2 glutamate transporter gene.[125,126] Furthermore, gp120 may increase glutamate toxicity on the other side of the equation as well, by stimulating release of glutamate from astrocytes.[127–129] Despite these effects on glutamate, however, NMDA receptor antagonists have failed to prevent gp120 associated neuronal cell death.[130]

Gp120 also induces production of inflammatory cytokines/chemokines, including TNF-α and IL-1,[128,131–134] from monocytes/macrophages,[135] and induces nitric oxide synthase, thus increasing oxidative stress.[136]

Nef

HIV requires Nef to bud from infected cells. Unlike Tat and gp120, Nef is not excreted and is not found extracellularly. It is localized primarily to the nucleus of infected cells, but is also found in the cytoplasm. However, when infected cells rupture, Nef will enter the extracellular milieu, where it potentially could cause direct neuronal damage. It can also cause indirect neuronal damage by altering the function of infected cells, thereby causing those cells to harm neurons. Furthermore, presence of Nef leads to astrocyte death[137] with resultant loss of glial support functions. In vitro, Nef is toxic to both neurons and glial cells.[138] Nef increases expression of matrix metalloproteinase (MMP)-9, which, in turn may disrupt the BBB[139] and have other neuropathological implications. Nef also causes astrocytes to express neurotoxic inflammatory mediators.[137] In one study, Nef-transduced macrophages were injected into rat hippocampus, and produced monocyte/macrophage recruitment, expression of TNF-α, astrogliosis, and behavioral changes in the rats, but no apoptosis of astrocytes or neurons.[140] Nef has sequence similarities to scorpion neurotoxins[141,142] and, like scorpion neurotoxins, can inhibit potassium channels.[143] Finally, Nef increases release of quinolinic acid, a glutamate-like excitotoxin.[144]

Nef may also be neuroprotective under certain conditions, or at least elicit a protective immune response from the host. One recent study showed that HIV infection upregulates microglial IL-16 production in a Nef-dependent manner.[145] IL-16 is previously known to have anti-HIV properties.

In any event, Nef expression is particularly abundant in the brains of HIV demented patients.[33,34] Nef may also play a role in spinal cord neurotoxicity. Transgenic mice expressing Nef in oligodendrocytes develop vacuolar myelopathy, suggesting that Nef prevents proper differentiation of oligodendrocytes and predisposes to development of HIV-associated vacuolar myelopathy.[146] Therefore, while little work has been directed in this area, Nef represents a potential therapeutic target for both HIV dementia and vacuolar myelopathy.

Virotoxin-Associated Phenomena

When virotoxins interact with and activate uninfected cells, the activated cells produce numerous proinflammatory factors, which in turn cause neuronal toxicity, but also cause further immune and glial cell activation, amplifying the initial effects of the viral proteins in a domino effect.[147] The inflammatory process can then be self-perpetuating, even if the viral proteins are eliminated and the virus is sequestered. This has been termed the hit and run phenomenon.[99] Viruses such as rabies, herpes simplex, and varicella zoster can travel within neuronal axons and dendrites using axonal transport mechanisms for their spread. Since neuronal axons stretch over long distances, this provides a relatively easy mechanism for dissemination of the virus throughout the nervous system. Whole HIV virus does not seem to spread in this manner, but Tat protein can be transported along neuronal pathways.[148] The ability of virotoxins to transport and cause toxicity at sites distant from the virus has been termed the trebuchet phenomenon.

Inflammatory host factors

Since neurons themselves are not infected,[36] a major mechanism by which viral mediators induce neuronal damage is by promoting production of host inflammatory mediators. Although HIV infection strongly induces normal host defense mechanisms, these defenses are ineffective and actually result in harm.[149] In fact, oxidative stress and production of certain cytokines enhance HIV replication.[150,151]

Chemokines

Chemokines are a specific family of cytokines identified by their ability to selectively modulate leukocyte trafficking in inflammatory processes, but also able to participate in numerous other processes involving cell-cell communication and signaling cascades.[152] The chemokine family consists of more than 40 members and is subdivided into four groups, named CXC, CC, CX3C, and C, according to the number of amino acids separating two cysteine residues within a highly conserved region of the chemokines. Chemokines exert their biological effects via interaction with G protein-coupled receptors, classified according to the group of chemokines to which they bind. They are named CXCR1-6, CCR1-11, CX3CR1, and XCR1.[153] Most chemokines bind to more than one receptor and most receptors bind to several chemokines.[154]

CX3CL1, also called fractalkine, and CXCL12, also called SDF-1, are the only chemokines constitutively expressed in the brain, principally by neurons and astrocytes, respectively.[155] However, many chemokine receptors have been identified on microglia from humans and rodents,[156–160] suggesting that chemokines play an important role in the regulation of microglia. Chemokines and their receptors are also involved in HIV-1 infection and migration into the brain. Chemokine receptors are coreceptors with CD4 for HIV-1 entry into target cells. Macrophage-tropic HIV-1 viruses use CCR5 as a coreceptor and T-cell line tropic HIV-1 viruses use CXCR4.

Dual-tropic viruses use both coreceptors.[161] HIV-1 then enters the brain within infected monocytes and CD4+ T-lymphocytes, which cross the BBB in response to signals from chemotactic chemokines, such as MCP-1/CCL2. For example, using an in vitro BBB model system, MCP-1 was demonstrated to be a primary chemoattractant for monocytes, and astrocytes, stimulated by proinflammatory cytokines, were shown to be the major source of MCP-1.[162] Certain polymorphisms in MCP-1 increase the risk of HIV dementia almost five fold.[163]

Postmortem studies have also revealed upregulation of some chemokines and chemokine receptors in the brains of patients with HIV and HIV encephalitis, in amounts and anatomic locations relevant to the severity and clinical symptoms of HIV encephalitis.[164] The expression levels of CCR1, CCR3, CCR5, and CXCR4 were all increased on macrophages/ microglia, especially in microglial nodules, in patients with HIV encephalitis.[164] The presence of MCP-1, MIP-WCCL3, and RANTES/ CCL5 has also been associated with the histopathological signs of HIV encephalitis.[165,166] Fractalkine is overexpressed in brain tissues of AIDS patients with HIV dementia compared to AIDS patients without HIVD.

Cytokines

Cytokines are proteins that regulate cells and tissues under either physiological or pathological conditions, mediate communication between cells, and are either proinflammatory or anti-inflammatory. In patients with HIV dementia, both proinflammatory and antiinflammatory cytokines are increased. They play a major role in the induction and regulation of inflammation in the central nervous system (CNS), thus producing or inhibiting neurotoxicity.[167] The cytokines present in the CNS are produced primarily by peripheral immune cells that have entered the brain, often across a defective BBB. Activated glial cells and even certain neurons may also produce cytokines. Cytokines interact with each other within a complex regulatory network, and many cytokines are undoubtedly involved in the neuropathogenesis of HIV infection. Several lines of evidence suggest that two of the most important cytokines in neuroinflammatory and neuroinfectious conditions, including HIV dementia, are tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β).

The viral Tat protein is even more potent then lipopolysaccharide in inducing TNF-α,[100] perhaps by upregulating the TNF-α promoter.[168] TNF-α has numerous effects that harm the host, and elevated levels of cerebrospinal fluid (CSF) and serum TNF-α seem to correlate with presence of dementia.[169] Concentrations of TNF-α mRNA and protein are significantly elevated in the brains of patients with HIV dementia.[170] The temporal profile of TNF-α expression correlates with the onset, progression, and severity of HIV dementia.[171] Polymorphisms of TNF-α are four times more frequent in patients with HIV dementia than in patients with HIV but no dementia.[172] TNF-α promotes formation of reactive oxygen species, inhibits glutamate uptake by glial cells,[173,174] induces other cytokines including IL-6 and IL-8,[175] upregulates expression of endothelial cell adhesion molecules,[176] and promotes HIV replication in microglial cells.[151] TNF-α triggers apoptosis via TNF receptors and excitotoxicity via AMPA receptors. TNF-α inhibitors reduce brain inflammation and neuronal injury in a murine model of HIV-1 encephalitis.[177]

The HIV-1 gp120 protein increases expression of IL-1β in primary glial cells, and this increase has been associated with neuronal cell death.[178] Treatment with either the

antioxidant, Trilox, or a neutralizing anti-IL-1β antibody could completely attenuate this neurotoxicity.[179] In adult rat brain, IL-1β exacerbates the neuronal damage induced by NMDA application,[180] and NMDA receptor blockade attenuates the proconvulsant effects of intrahippocampal injection of IL-1β in rats.[181] Inhibition of endogenous IL-1 and TNF-α, by the natural IL-1 receptor antagonist, the soluble TNF-α receptor, or neutralizing antibodies, markedly attenuates neuronal damage in neurodegenerative conditions.[180,182]

Despite this evidence, there is still some controversy about the role of these cytokines in HIV dementia, because a few studies have indicated a neuroprotective role for both TNF-α and IL-1β in certain conditions.[183–185] For example, TNF-α knock-out animals suffer more severe neuronal damage then controls in some studies.[186] These conflicting data are likely due to the complex nature of the interactions between cytokines. The effect of cytokines can vary due to many factors such as the combinations and concentrations of other cytokines present at the same time, and even the temporal sequence of the same cytokines acting on the same cell.

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a family of endopeptidases that enzymatically degrade extracellular matrix (ECM) proteins and can thus disrupt the BBB and neuronal synapses.[49,187–190] Matrix metalloproteinase levels are elevated in the CSF of patients with HIV dementia.[191] Matrix metalloproteinases can cleave chemokines, such as SDF-1, with the cleavage products subsequently causing neurotoxicity,[192] and they can interact with integrin receptors on neurons, initiating apoptosis.[193] Furthermore, they can become nitrosylated and hyperactive, contributing to neurotoxicity under conditions of oxidative stress.[194] Tat can induce MMP expression in monocytes[195] and in mixed neuronal-glial cultures,[196] which might facilitate monocyte transmigration through the extracellular matrix. HIV infection may also impair the ability of astrocytes to secrete tissue inhibitors of MMPs and thus control the damaging effects of MMPs.[197,198]

However, MMPs may also have neuroprotective effects. Cleavage of MCP-3 by MMP-2 has been shown to decrease the inflammatory response.[199] MMPs-1, -2, and -9 were also found to be neuroprotective in an in vitro HIV dementia model system.[200] MMP-1 specifically was found to cleave the neurotoxic viral protein, Tat. Specific MMP inhibitors, or in some cases even MMP augmentors may be required for therapeutic targeting of MMP pathways in HIV dementia.

Oxidative and Nitrosative Stress

Oxidative stress is an important mechanism for neurotoxicity in many inflammation-mediated neurodegenerative diseases.[201–203] Free radicals including superoxide anion, hydroxyl radical, lipid hydroperoxides, hydrogen peroxide, nitric oxide, and perinitrite, are produced in order to kill invading pathogens, but are also toxic to neurons by causing lipid peroxidation, DNA fragmentation, and protein oxidation,[204] and by activating signaling cascades that regulate other proinflammatory factors.[205,206] Active replication of HIV-1 in macrophages and microglia leads to the production of inflammatory products including free radical species.[207–209] Patients with HIV infection not only have increased production of oxidative stress, but also depletion of endogenous antioxidants.[210,211]

Superoxide is produced by myeloid-monocytic cell lines following HIV-1 infection or treatment with HIV proteins, such as gp120.[212] Nitric oxide is released by neurons or glia in response to excitatory neurotransmission, changes in calcium homeostasis, and treatment with inflammatory cytokines or HIV proteins like Tat.[213,214] HIV-1 infection upregulates inducible nitric oxide synthase (iNOS) expression in brain tissues both directly and indirectly through proinflammatory cytokines, such as IL-1β and TNF-α.[209,215] Although it enhances glutamate release[216] and inhibits glutamate uptake,[217,218] thus inducing excitotoxicity, the neurotoxic effects of nitric oxide alone are relatively small. Also, superoxide dismutase, a superoxide anion scavenger, keeps the concentration of superoxide low.[219] Together, however, superoxide and nitric oxide have synergistic neurotoxicity by reacting with each other to form peroxynitrite, a potent oxidant that is responsible for nitration of tyrosine residues of many proteins. For example, nitration disrupts neurofilament assembly, inducing neuronal damage.[219,220]

Cyclooxygenases and Prostaglandins

There are two isoforms of cyclooxygenase (COX-1 and COX-2) that convert arachidonic acid to hydroxyl-endoperoxide, which is then metabolized to various prostaglandins.[221] COX-1 is constitutively expressed,[221,222] while COX-2 is induced by cytokines and other inflammatory factors, and plays an important role in inflammation.[222,223] In vitro co-culture of HIV-infected macrophages with brain-derived endothelial cells causes up-regulation of COX-2 expression by both cell types, suggesting that interactions between HIV-infected monocytes and brain endothelial cells may result in COX-2 expression and contribute to the neuropathogenesis of HIV-1 infection.[224] The up-regulation occurs via an IL-1β-dependent mechanism in macrophages and via an IL-1β-independent mechanism in endothelial cells. In gp120-treated human neuroblastoma cells, increased COX-2 expression and subsequent cell death can be attenuated by inhibitors of IL-1 converting enzyme, and gp120 mediated neurotoxicity can be attenuated by a COX-2 inhibitor, NS-398.[225]

As with other proinflammatory factors, there is debate about the role of COX-2 and prostaglandins in neurodegeneration. Under certain conditions, COX-2 inhibition results in enhanced neurodegeneration.[226–227] These conflicting results may be explained by the effects of different prostaglandin products working through different receptors, or by interactions with the complicated network of other proinflammatory factors.[228]

Other host factors

Growth Factors

Insulin-like growth factor (IGF)-1,[229] nerve growth factor (NGF) and β-fibroblast growth factor (FGF)[230] may all have protective effects against HIV-induced neurotoxicity. However, brain derived neurotrophic factor (BDNF) has perhaps received the most attention as a possible therapeutic option in HIV dementia. Gp120 mediates neuronal apoptosis through caspase-3 and BDNF prevents caspase-3 mediated neuronal cell death. Incubation of rat cerebellar neurons with BDNF prior to addition of gp120 reduced caspase-3 activation and rescued 80% of neurons from apoptosis.[231] In the same study, BDNF was also shown to reduce levels of CXCR4, a receptor through which both gp120 and SDF-1 can cause neurotoxicity. In an in vivo study, mice with heterozygous knockout of BDNF sustained greater neuronal damage from intracerebral gp120 injection than wild type littermates.[232] Gp120 itself may reduce BDNF levels in rat brain.[232]

Lipids and Apolipoprotein E

Apolipoprotein E (apoE) polymorphisms have been implicated in susceptibility for development of several neurological diseases, including Alzheimer's disease and HIV dementia. Interestingly, both apoE and the HIV Tat protein bind to the low-density lipoprotein receptor related protein (LRP).[86] Patients with HIV dementia and an apoE3/4 or apoE4/4 genotype have elevated brain levels of sphingomyelin, ceramide, and cholesterol, compared to those with an apoE3/3 genotype.[233] In vitro exposure of neurons to gp120 and Tat also increases levels of sphingomyelin and ceramide, and sensitizes neurons to Tat and gp120 toxicity, while an inhibitor of ceramide production is neuroprotective against the effects of Tat and gp120.[234] In response to treatment with Tat, ex vivo synaptosomes from apoE-knockout mice have smaller elevations of reactive oxygen species and protein oxidation, and less reduction in mitochondrial membrane potential, than synaptosomes from wild type mice, while apoE3 protected in vitro human neurons from Tat, through antioxidant properties.[235] ApoE4 was not protective. Overall, these results suggest that the apoE may contribute to HIV neuropathogenesis by modifying neuronal lipid metabolism, in such a way as to sensitize neurons to the effects of Tat and gp120.

Implications for haart

Highly active antiretroviral therapy has proven extremely effective in the control of HIV infection. Highly active antiretroviral therapy consists of a regimen of multiple antiretroviral medications. Combination therapy is required in order to prevent emergence of viral resistance to therapy, and thus provide a lasting suppression of viral replication. The viral DNA polymerase, reverse transcriptase, lacks a 3' to 5' exonuclease proofreading mechanism and is highly error prone.[236] As a result, an average of one mutation is inserted

into every three HIV copies, which means that multiple mutations are inserted into every position of the HIV genome every single day.[237] The mutated viruses have varying degrees of susceptibility to the individual antiretroviral agents, explaining the requirement for combination therapy, to minimize the possibility of mutation to a strain that is not targeted by any of the therapies. Viral load testing is routinely used to ensure the effectiveness of antiretroviral therapy. Many of these medications are currently available as part of combination pills, introduced to ease compliance with the complicated regimens required by combination therapy.

This chapter focuses on treatment of the neurological complications of HIV infection, and, as such, a detailed description of treatment strategies for HIV/AIDS is beyond its scope. Several consensus guidelines are available, however, including those from the United States Department of Health and Human Services[238] and from the International AIDS Society.[239] These recommendations are summarized in Table 17–2. Important characteristics of the currently available antiretroviral agents are summarized in Table 17–3.

Table 17–2 Recommended Antiretroviral Regimens for Treatment of HIV-1 Infection in Antiretroviral Naïve Patients Based on Department of Health and Human Services Guidelines[238]
Preferred Regimens
Non-nucleoside RT-inhibitor based efavirenz + (emtricitabine or lamivudine) + (tenofovir or zidovudine)
Protease inhibitor based (emtricitabine or lamivudine) + lopinavir/ritonavir+zidovudine
Alternative Regimens
*Non-nucleoside **RT**-inhibitor based* (abacavir or didanosine or stavudine) + efavirenz + (emtricitabine or lamivudine) (abacavir or didanosine or stavudine or tenofovir or zidovudine) + (emtricitabine or lamivudine) + nevirapine
Nucleoside RT-inhibitor based abacavir + lamivudine + zidovudine
Protease inhibitor based (abacavir or didanosine or stavudine or tenofovir/ritonavir or zidovudine) + atazanavir + (emtricitabine or lamivudine) (abacavir or didanosine or stavudine or tenofovir or zidovudine) + (emtricitabine or lamivudine) + fosampren avir (abacavir or didanosine or stavudine or tenofovir or zidovudine) + (emtricitabine or lamivudine) + fosampren avir/ritonavir (abacavir or didanosine or stavudine or tenofovir) + (emtricitabine or lamivudine) + lopinavir/ritonavir (abacavir or didanosine or stavudine or tenofovir or zidovudine) + (emtricitabine or lamivudine) + nelfinavir (abacavir or didanosine or stavudine or tenofovir or zidovudine) + (emtricitabine or lamivudine) + saquinavir/ ritonavir

Table 17–3 Characteristics of Currently Available Antiretroviral Agents

Drug	Typical Dose[a]	Half-life (Hours)[b]	Oral Bioavailability[c]	CSF Penetrance[d]	IC50 (nM)[e]
Non-Nucleoside RT Inhibitors					
delavirdine	400 mg TID	6	85	0	40
efavirenz	600 mg QHS	48	40	<2	2.5
nevirapine	200 mg BID	24+	90	45	250
Nucleoside RT Inhibitors					
abacavir	300 mg BID	12	80	30	250
didanosine	200 mg BID	24+	40	20	10000
emtricitabine	200 mg QD	40	90		10
lamivudine	300 mg QD	18	85	10	70
stavudine	40 mg BID	3.5	85	30	1000
tenofovir	300 mg QD	48+	25		8500
zalcitabine	0.75 mg TID	3	85	20	140
zidovudine	300 mg BID	3	60	60	2000
Protease Inhibitors					
amprenavir	1200 mg BID	10		0	400
atazanavir	400 mg QD	6	65		5
fosamprenavir	1400 mg BID	8			400
indinavir	800 mg TID	2	65	<5	100
lopinavir	400 mg BID	5	80	0	300
nelfinavir	1250 mg BID	4	80	0	200
ritonavir	600 mg BID	4	80	0	150
saquinavir	1000 mg BID	7	4	0	40
tipranavir	500 mg BID	5			70
Fusion Inhibitors					
enfuvirtide	90 mg BID	4	0		100

[a] TID = three times daily; QHS = in the evening; BID = two times daily; QD = once daily.

[b] Serum half-life for non-nucleoside RT inhibitors and protease inhibitors, cellular half life for nucleoside RT inhibitors.

[c] Percent absorption from gastrointestinal tract.

[d] Percent spinal fluid level versus serum level.

[e] Nanomolar concentration required to produce 50% inhibition of viral growth.

Nucleoside Reverse Transcriptase Inhibitors

Following HIV entry into a cell, a viral RNA-dependent DNA polymerase, called reverse transcriptase (RT), forms a double stranded DNA copy of the viral RNA. Nucleoside reverse transcriptase inhibitors were the first class of medication successfully introduced for the treatment of HIV infection. Nucleoside RT inhibitors include abacavir (Ziagen), didanosine (ddI, Videx), emtricitabine (Emtriva), lamivudine (3TC, Epivir), stavudine (d4T, Zerit), zalcitabine (ddC, Hivid), zidovudine (AZT, Retrovir), and tenofovir (Viread). Tenofovir is actually a nucleotide analogue and contains a phosphate group.

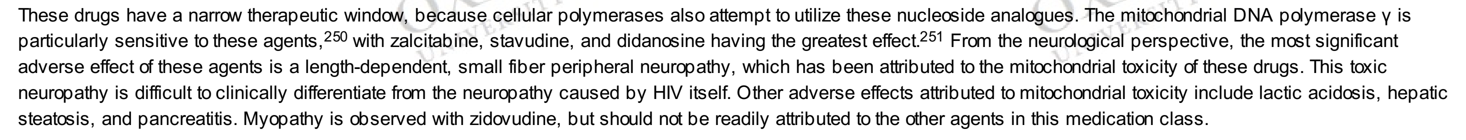
Nucleotides are the building blocks used by DNA (or RNA) polymerases, including reverse transcriptase, to make nucleic acids. Nucleotides consist of a sugar molecule linked to a nitrogenous base and a phosphate group. Nucleosides differ from nucleotides only in that they lack the phosphate group. In DNA, the nitrogenous bases are

adenine, thymine, guanine, and cytosine and the sugar molecule is deoxyribose. An RNA molecule uses uracil instead of thymine and ribose instead of deoxyribose. Nucleoside RT inhibitors are analogues of the naturally occurring nucleosides, and, as such, are competitive inhibitors of reverse transcriptase. When the nucleosides enter a cell, kinases must convert them into the triphosphate form before they can have their antiretroviral effect (tenofovir only requires conversion to a diphosphate form).[240] Then, when reverse transcriptase attempts to use them, they are unable to form phophodiester linkages, causing early termination of viral DNA chains.[241]

The dosing frequency of the nucleoside RT inhibitors is based on the half life of the intracellular phosphorylated form of the molecule, which is significantly longer then the serum half life of the prodrug.[242] Zidovudine and stavudine are currently used on a twice daily basis, while single daily dosing is possible with the other agents in this drug class. Once daily antiretroviral regimens are summarized in Table 17–4. Metabolism of this class of drug typically occurs primarily through renal excretion of unchanged drug, although zidovudine and abacavir undergo significant glucuronidation in the liver. Abacavir is also metabolized by the alcohol dehydrogenase enzyme, so use of alcohol increases serum abacavir levels by about 40%.[243] Bioavailability ranges from a low of about 25% for tenofovir[244] to a high of over 80% with lamivudine[245] and stavudine.[246] Zidovudine and didanosine should be taken on an empty stomach. Cerebrospinal fluid penetration is best for zidovudine, with CSF levels being 60% of serum levels. Stavudine and abacavir also seem to penetrate CSF well. Cerebrospinal fluid levels of lamivudine are only about 10% of serum levels, but this is still above the IC50 concentration for clearance of HIV RNA from CSF.[247] Penetration of the nucleoside RT inhibitors into the brain and CSF is likely mediated by organic acid transport systems, although their clinical importance is not fully defined.[248,249].

Table 17–4 Once Daily Antiretroviral Regimens
Non-Nucleoside RT Inhibitors
efavirenz
nevirapine[a]
Nucleoside RT Inhibitor Combinations
abacavir/didanosine
abacavir/emtricitabine
abacavir/lamivudine
abacavir/tenofovir
didanosine/emtricitabine
didanosine/lamivudine
didanosine/tenofovir
emtricitabine/tenofovir
lamivudine/tenofovir
Protease Inhibitors
atazanavir
atazanavir/ritonavir
fosamprenavir/ritonavir
lopinavir/ritonavir
saquinavir/ritonavir[a]

[a] Not FDA approved for once daily dosing



These drugs have a narrow therapeutic window, because cellular polymerases also attempt to utilize these nucleoside analogues. The mitochondrial DNA polymerase γ is particularly sensitive to these agents,[250] with zalcitabine, stavudine, and didanosine having the greatest effect.[251] From the neurological perspective, the most significant adverse effect of these agents is a length-dependent, small fiber peripheral neuropathy, which has been attributed to the mitochondrial toxicity of these drugs. This toxic neuropathy is difficult to clinically differentiate from the neuropathy caused by HIV itself. Other adverse effects attributed to mitochondrial toxicity include lactic acidosis, hepatic steatosis, and pancreatitis. Myopathy is observed with zidovudine, but should not be readily attributed to the other agents in this medication class.

Tenofovir and abacavir have unique adverse effects that are important to note. Tenofovir rarely causes renal failure due to proximal tubular necrosis, particularly in patients with preexistent renal insufficiency.[252] Discontinuation of tenofovir typically leads to resolution of the renal failure. Abacavir causes a serious hypersensitivity reaction, including fever, gastrointestinal distress, rash, fatigue, and sometimes dyspnea, in up to 8% of patients. Median time of onset is about 10 days and almost 95% of cases occur within the first six weeks of treatment.[253] Risk factors for the hypersensitivity reaction have been explored, with the most prominent being an association with HLA-B****5701.[254] Abacavir must be discontinued and not reused in any patient who develops hypersensitivity, because doing so frequently leads to an even worse reaction, including hypotension, respiratory insufficiency, and death, despite aggressive life-supporting measures.[253]

Non-Nucleoside RT Inhibitors

Like nucleoside RT inhibitors, the non-nucleoside RT inhibitors target the viral reverse transcriptase and production of viral DNA. However, they do not require activation after administration, and they are not nucleoside analogs. Rather, they are a diverse group of agents that all bind to reverse transcriptase with high specificity at sites distant from the nucleoside binding site, producing allosteric changes in the RT, and leading to potent noncompetitive inhibition of RT's ability to convert viral RNA to DNA. Due to their specificity, non-nucleoside RT inhibitors do not have activity against HIV-2 or group O strains of HIV-1.[255] Non-nucleoside RT inhibitors include delavirdine (Rescriptor), efavirenz (Sustiva), and nevirapine (Viramune).

Delavirdine has a half-life of about six hours and is dosed three times per day. Neviripine has a half-life of 25–30 hours, but single daily dosing causes an increase in side effects, so it is typically used on a twice daily schedule with a dose escalation over the first two weeks of therapy.[256,257] Efavirenz has a half-life of 40–55 hours and is used once daily. All three of these drugs are metabolized by hepatic cytochrome P450 (CYP3A4) prior to their excretion in the urine.[258] Nevirapine and efavirenz are autoinducers, while delavirdine inhibits its own metabolism. Efavirenz also undergoes some glucuronidation in the liver. Care must be used with these drugs, because of the possibility of drug-drug interactions. Levels of drugs metabolized by CYP3A4 may increase or decrease with coadministration of other drugs metabolized by CYP3A4.

Nevirapine induces cytochrome P450, delavirdine inhibits cytochrome P450, and efavirenz has mixed effects depending on the specific drugs with which it is used. Special consideration must be given to coadministration of non-nucleoside RT inhibitors with protease inhibitors. The issue of drug interactions in the treatment of HIV infection has been reviewed in detail.[259] Bioavailability of delavirdine and neviripine is around 90%, while that of efavirenz is around 40%. High fat meals significantly increase absorption of efavirenz, and therefore should be avoided. Efavirenz is also greater than 99% protein bound.[258] Cerebrospinal fluid penetration is best for nevirapine, with CSF levels being about 40% of serum levels. Cerebrospinal fluid penetration of delavirdine is minimal.[260] Cerebrospinal fluid levels of efavirenz are less than 2% of serum levels, but this is still above the IC95 concentration for clearance of HIV RNA from CSF.[261]

Significant adverse effects with this class of medication include the following. Hepatotoxicity occurs with all three drugs, usually within the first twelve weeks of therapy, with the greatest risk being in woman with CD4 counts over 250 cells/pL taking nevirapine.[262] Risk is also increased in those with preexistent hepatic disease and in those on other hepatotoxic medications.[263] All three drugs also cause rash, usually within the first eight weeks of therapy, with nevirapine being the worst offender. Nevirapine causes a rash

in up to 50% of patients, which can become severe in around 10%, and can progress to Stevens-Johnson syndrome in around 1%.[264,265] Frequently, these medications will be stopped when a rash appears, especially if accompanied by fever, blisters, arthralgias, or mucous membrane involvemnent, but often can be restarted without dose reduction after the rash resolves. Efavirenz has the lowest frequency of rash at about 10%, but causes CNS toxicity in up to 50% of patients upon initiation of therapy, and therefore should be dosed at bedtime. Symptoms include vivid dreams, visual hallucinations, confusion, poor concentration, dizziness, somnolence, insomnia, and euphoria. There may be additive effects with alcohol and other psychoactive medications. These symptoms usually resolve within four weeks of therapy, and are severe enough to force discontinuation of the drug in only 2%–5%.[266]

Protease Inhibitors

The double stranded DNA formed by reverse transcriptase is subsequently integrated into the cellular genome by a viral protein known as integrase. Integrase inhibitors are currently under development, but none are yet available for clinical use. Integrated viral DNA is used to produce messenger RNA that encodes for viral proteins. The viral proteins are produced in the form of polyproteins, consisting of several viral proteins joined end to end. The viral protease cleaves these proteins from each other, forming individual, functional proteins. Protease inhibitors prevent cleavage of viral proteins after viral budding, thereby preventing infection of new cells.[267] The addition of these drugs to the reverse transcriptase inhibitors has dramatically reduced the mortality of HIV infection over the last 10 years.[268] Protease inhibitors include atazanavir (Reyataz), fosamprenavir (Lexiva), indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Fortovase, Invirase), tipranavir (Aptivus), and lopinavir. The latter is only available clinically in combination with ritonavir (Kaletra).

The serum half-lives of protease inhibitors are short, ranging from one hour for saquinivir to seven hours for atazanavir,[238] so they typically must be dosed two or three times daily. These drugs are essentially all metabolized in the liver by cytochrome P450 (mostly CYP3A4) and/or glucuronidation (particularly indinavir). To simplify the dosing schedule, they are frequently combined with of low doses of ritonavir, about 100 to 200 mg. Ritonavir inhibits cytochrome P450 metabolism, thereby allowing once or twice daily dosing. Ritonavir is not a very potent protease inhibitor, and in such combinations, it is primarily being used for its drug metabolism effects and not for its antiretroviral effects. Once again, because of their metabolism in the liver, care must be used with protease inhibitors due to the possibility of drug-drug interactions.[259] Bioavailability ranges from about 5% with saquinavir to 80% with lopinavir. Taking these medicines with food is generally allowed or even preferred. The exception is indinavir, the absorption of which is significantly decreased by food. Indinavir, therefore, should be taken on an empty stomach or along with ritonavir, which will maintain indinavir serum levels regardless of food. Cerebrospinal fluid penetration is best for indinavir, with CSF levels being only about 10% of serum levels. However, this is still above the IC95 concentration for clearance of HIV RNA from CSF,[269] it can be increased even further by coadministration of ritonavir, and is far superior to that of other protease inhibitors,[270] which have almost no CSF penetration.[271] Penetration of protease inhibitors into the brain is minimized due to their active efflux by p-glycoproteins on brain endothelial cells.[272]

The most significant adverse effects with this class of medication are hyperlipidemia, lipodystrophy, and insulin resistance.[273] Atazanavir may have less of these effects, and is therefore frequently used in patients with preexistent dyslipidemia.[274] It is very important to monitor for dyslipidemia and impaired glucose metabolism in any patient on a protease inhibitor and treat with cholesterol and/or glucose lowering agents, as appropriate. Lipodystrophy refers to altered body fat distribution, typically with central fat accumulation and loss of fat from the face, buttocks, and extremities. This side effect is most common in patients on a regimen containing two nucleoside RT inhibitors and one protease inhibitor. Optimal management, and even the longer term health consequences beyond physical appearance and social stigmatization, are still not well defined.[275] Protease inhibitors are also commonly associated with gastrointestinal side effects, which may limit adherence to the medication.[267] Indinavir is associated with nephrolithiasis,[276] and both indinavir and atazanavir are associated with hyperbilirubinemia.[277] The liver effects usually do not require discontinuation of the drug. Most patients with indinavir-induced nephrolithiasis have elevated peak indinavir serum levels, and can maintain virological suppression without nephrolithiasis at a reduced indinavir dose.[278]

Fusion Inhibitors

After HIV binds to a cellular surface, fusion of the viral envelope with the cellular membrane occurs, leading to insertion and uncoating of the viral nucleocapsid. This step in the viral life cycle is the target of the most recent addition to our armamentarium against HIV, the fusion inhibitor, enfuvirtide (T20, Fuzeon). Two large, multicenter, randomized, clinical trials have demonstrated the efficacy and safety in adults[279,280] and children[281,282] who had failed all previously available anti-HIV regimens and/ or had very restricted antiviral options due to multiclass antiretroviral resistance of the infecting HIV strain. These trials were open-label, but the primary end-point was change from baseline in serum HIV RNA level, and analysis was done on an intention-to-treat basis. Resistance to other antiretroviral drugs does not cause resistance to enfuvirtide.[283] Resistance to enfuvirtide is associated with mutation in the HR1 domain of gp41,[284,285] one of the HIV envelope proteins involved in viral fusion. Enfuvirtide is a synthetic analog of the HR2 domain of gp41, but the exact mechanism by which enfuvirtide prevents fusion is unknown.[286] Enfuvirtide is significantly less potent against HIV-2 than it is against HIV-1, although it seems effective against all strains of HIV-1.[287]

The half-life of enfuvirtide is approximately four hours and it is dosed on a twice daily basis. It must be administered as a subcutaneous injection because it is a polypeptide, consisting of 36 amino acids, which would be digested in the stomach. Metabolism is by catabolism to component amino acids, and enfuvirtide has no effect on cytochrome P450.[288] The potential for drug-drug interactions is therefore minimal. Bioavailability of subcutaneous dosing is about 85% compared to intravenous dosing.[289] The CSF penetration of enfuvirtide is unknown, but, as a polypeptide, it is unlikely to cross the blood-brain barrier well. Other than injection site reactions, which occurred in 98% of clinical trial participants but were rarely severe enough to limit or discontinue treatment, adverse reactions to enfuvirtide were rare.[286,290,291] More information about significant adverse reactions is likely to become apparent through post-marketing surveillance.

Implications for HAART in the Treatment of HIV-Associated Neurological Complications

Brain tissue levels of medications are not easily measured. Therefore, CNS penetration is assumed, based on CSF concentration. However, the level of drug in brain does not depend only on CSF concentration, but also on plasma concentration, protein binding, the intrinsic ability of the drug to pass through the blood brain barrier, and the possibility of transporter proteins.[272,292] Additionally, patients with HIV dementia may have breakdown of the BBB, allowing easier access for agents that would not normally accumulate in the brain.[293] Furthermore, antretroviral CSF concentration determinations are often based on only a few patients and can vary widely. Nevertheless, drugs that are considered to be CNS penetrating are those that achieve CSF concentrations greater than the median 50% inhibitory concentration for HIV replication. These include the nucleoside reverse transcriptase inhibitors, zidovudine, stavudine, and abacavir, the non-nucleoside reverse transcriptase inhibitors, nevirapine and efavirenz, and the protease inhibitor, indinavir, all of which have performed well for HIV dementia in clinical trials.[269,294–299] Combinations of these drugs should therefore be considered first-line for treatment and prophylaxis of HIV dementia,[300] although the optimal HAART regimen is still not rigorously defined. Possible CNS penetrating regimens for consideration in the treatment or prophylaxis of HIV dementia are listed in Table 17–5.

Table 17–5 Central Nervous System Penetrating Antiretroviral Regimens for Treatment or Prophylaxis of HIV Dementia
Non-nucleoside RT-inhibitor based
efavirenz + lamivudine + zidovudine
(abacavir or stavudine) + efavirenz + lamivudine
(abacavir or stavudine or zidovudine) + lamivudine + nevirapine
Nucleoside RT-inhibitor based
abacavir + lamivudine + zidovudine
lamivudine + stavudine + zidovudine[a]
Protease inhibitor based
(abacavir or stavudine or zidovudine) + indinavir + lamivudine[a]
(abacavir or stavudine or zidovudine) + indinavir/ ritonavir + lamivudine[a]
(abacavir or stavudine) + lamivudine + lopinavir/ ritonavir
lamivudine + lopinavir/ritonavir + zidovudine

[a] This regimen is not recommended by Department of Health and Human Services Guidelines[238]





Impact of HAART on Cognitive Function in HIV-Infected Patients

Reliance on HAART to control HIV dementia is not adequate. A recent study[301] evaluating neuropsychological performance in seven cognitive domains suggests that HAART has little effect on many of the cognitive domains impaired by HIV dementia. HAART may improve memory loss, but only after a certain threshold of neuropsychological impairment has been reached. In this study, HIV-positive individuals were significantly impaired versus controls, despite the use of HAART for an average of 18.5 months. The use of a HAART regimen that included CNS-pentrating drugs did not affect performance compared to regimens without these drugs, except in the group of patients already diagnosed with HIV dementia, in whom a CNS-penetrating regimen was associated with significantly better memory performance. HAART has reduced the incidence of severe forms of HIV associated dementia, but milder forms persist. HAART has also allowed patients to live longer with HIV infection, and the prevalence of HIV dementia is actually rising.[1–5] Additionally, HIV dementia continues to be a marker of poor prognosis in HIV infection. Almost 10% of patients who attended one public HIV clinic and died between 1996 and 2001, after the introduction of HAART, died with HIV dementia, and, of those, over 90% were diagnosed with HIV dementia within 12 months of death from HIV.[302]

Cerebrospinal fluid HIV RNA levels have been used as an indication of treatment efficacy in the CNS. Although this correlation has not been definitively demonstrated, improvements in neuropsychological testing after initiation of HAART correlate with decline in CSF viral load, while those patients with no CSF viral load decline also had no neuropsychological improvement.[303–305] Recent work demonstrated that patients receiving a greater number of the above listed CSF penetrating drugs showed significantly greater reduction in CSF viral load. There was not a direct linear correlation between number of penetrating drugs, CSF viral load, and neurocognitive performance, but those who attained an undetectable CSF viral load showed greater improvement on a battery of neuropsychological tests than those who did not.[306]

Drugs That May Exacerbate HIV Dementia

Certain drugs must be avoided or used cautiously in patients with HIV dementia (see Table 17–6). Antipsychotic drugs and antiemetics that antagonize dopamine receptors can precipitate parkinsonism in patients with HIV dementia.[307,308] The use of valproate in these patients is controversial. Some studies suggest it has neuroprotective properties,[309–311] while others suggest it enhances viral replication.[312,313] Any drug that induces activity of cytochrome P450 can increase the metabolism of some protease inhibitors, leading to inadequate control of viral replication. For neurologists, anticonvulsants are a primary concern in this regard, but the possibility of drug interactions must be carefully considered whenever adding a new medicine to the regimen of a patient on a protease inhibitor. Such medicines can typically still be used, but the dosage of the protease inhibitor often requires adjustment and the viral load must be carefully monitored during the transition period.[259]



Table 17–6 Drugs to be Used Cautiously in Patients with HIV Dementia
Cytochrome P450 inducers • Antibiotics Isoniazid Rifampin • Anticonvulsants Carbamezapine Ethosuximide Phenobarbital Phenytoin • Omeprazole • Steroids Dexamethasone Prednisone
Dopamine receptor antagonists • Antipsychotics Chlorpromazine Clozapine Haloperidol Olanzapine Risperidone • Antiemetics Domperidone Metoclopramide
Valproate

Implications for drug development

Currently, the standard of care for patients with HIV dementia is to optimize control of serum viral load using HAART. As has been recently reviewed[314] and summarized in Table 17–7, numerous new agents are being developed as additions to the HAART repertoire, to even better control serum viral load, and, by extension, to better control HIV associated neurotoxicity. This includes new reverse transcriptase inhibitors and new protease inhibitors. It also includes entry inhibitors with various mechanisms: attachment inhibitors, coreceptor binding antagonists, and fusion inhibitors. The only currently available entry inhibitor, enfuvirtide, is a fusion inhibitor, and there are no other promising fusion inhibitors beyond preclinical study. Attachment inhibitors prevent binding of gp120 to CD4. Within this class, there are both monoclonal antibodies and small molecule inhibitors currently undergoing early clinical trials. Coreceptor binding antagonists inhibit interaction of HIV with either CCR5 or CXCR4. CCR5 antagonists appear more promising because the majority of HIV strains utilize CCR5, and people with CCR5 deficiency appear to have no clinical adverse effects, while CXCR4 is known to be critical to embryogenesis[315] and CXCR4 antagonism may impair critical intracellular communication or other functions. Unfortunately, HIV tropism appears to shift from CCR5 predominance to CXCR4 predominence as the disease progresses and CD4 counts drop, suggesting that such a shift may also occur when the virus is exposed to a CCR5 antagonist. Other classes of antiretrovirals currently in development include integrase inhibitors and maturation inhibitors. Several classes of integrase inhibitors, with different characteristics, are being studied.[316] There is only one maturation inhibitor, called PA-457, currently being studied. It interferes with conversion of the capsid precursor, p25, to the mature capsid protein, p24. Without p24, virions are noninfectious because of defective core condensation.[317]

Table 17–7 Investigational Antiretroviral Agents in Clinical Trials

Agents	Development phase
Attachment inhibitors	
BMS-378806	I
BMS-488043	I/II
dextrin 2-sulphate	I
peptide T	II
PRO 542	II
R15K	I
TNX-355	II





CCR5 antagonists	
ALX40–4C	I
aplaviroc	III
maraviroc	II/III
PRO 140	I/II
SCH-C	II
TAK-779	I
Vicriviroc	III
CXCR4 antagonists	
AMD-3100	III
NSC651016	I
Fusion inhibitors	
T-1249	II
Gag antisense inhibitors	
GEM-91	I
Integrase inhibitors	
L-870810	I
S-1360	II
zintervir	I
Maturation inhibitors	
PA-457	II
Non-nucleoside RT inhibitors	
BILR 355 BS	I
calanolide A	II
capravirine	II
dapivirine	II
DPC 083	II
DPC 961	II
DPC-9 63	I
etravirine	III
GSK695634	II
GW678248	II
NSC678248	I
rilpivirine	I/II
Nucleos/tide RT inhibitors	
adefovir dipivoxil	II/III

alovudine	II
amdoxovir	II
AVX754	II
dexelvucitabine	II
dioxolane thymidine	II
elvucitabine	I
emivirine	III
GS-7340	I
KP-1461	I
lobucavir	I
lodenosine	II
MIV-210	I/II
racivir	I/II
SPD756	I
Protease inhibitors	
brecanavir	II
darunavir	III
DMP323	I
doxovir	I
DPC-681	I
DPC-684	I
L756,423	II
mozenavir	II
PD-178390	I
TMC126	I
P24 capsid inhibitors	
GPG-NH2	II
Zinc finger nucleocapsid inhibitors	
Azodicarbonamide	II
CI-1012	I

This chapter will focus on agents that may specifically prevent the neurotoxicity of HIV. For multiple reasons discussed in this chapter, including the poor CNS penetration of many HAART agents, and the inability of HAART to target many of the mediators of neurotoxicity in HIV dementia, HAART alone is inadequate. Neuroprotective strategies must be employed based on the current understanding of HIV neuropathogenesis, as detailed in this chapter. There are no neuroprotective drugs clinically available for treatment of HIV dementia, but the neuropathogenic mechanisms suggest several possible targets (see Table 17–8).[318]



Table 17–8 Possible Neuroprotective Agents in HIV Dementia
Antioxidants diosgenin glutathione analogs resveratrol selegiline selenium
Calcium channel blockers nimodipine
Erythropoietin
GSK3β inhibitors lithium valproate
MMP inhibitors minocycline statins
Monoclonal antibodies
NMDA antagonists amiloride ceftriaxone memantine pentamidine
Potassium channel blockers
Small interfering RNAs
TNF antagonists pentoxyfylline thalidomide

Antioxidants

The monoamine oxidase B inhibitor and antioxidant, selegiline, is one of the few putative neuroprotective agents to have demonstrated in two small studies clinical benefit for patients with HIV dementia.[319,320] The first study evaluated 36 patients and the second study included nine patients. Both studies used randomized, double-blind, placebo-controlled designs and found better performance on recall and psychomotor processing tests at 10 weeks in patients taking selegiline compared to those who were not. The results were consistently in favor of selegiline, although not statistically significant for most of the individual cognitive tests. However, the studies were underpowered for this purpose, and the first study failed to show any favorable trends for another drug, thiotic acid.

A recent in vitro study found several other antioxidants that can block the oxidative stress produced when neurons are treated with CSF from patients with HIV dementia,[203] including estrogen-like agents, selenium, and glutathione mimics. Plant phytoestrogens, such as diosgenin and resveratrol, have in vitro neuroprotective properties, without the carcinogenic and feminizing properties of animal estrogens.[203,321] Synthetic estrogens could also be designed in an effort to provide benefit without severe adverse effect. Glutathione is an endogenous antioxidant that is reduced in HIV-infected individuals.[92,115] N-acetylcysteine, widely available as a mucolytic agent in respiratory diseases,[322] is a glutathione precursor, and has been shown to decrease TNF levels in the serum of HIV infected individuals, and to slow the rate of decline of CD4 counts.[323] A similar glutathione precursor, called AD-4, from Nova Pharmaceuticals, in Tel Aviv, Israel, has much better CNS penetration than N-acetylcysteine.

Anti-TNF Therapies

There are several anti-TNF-α agents currently available, including pentoxifylline and thalidomide, which may be beneficial in HIV dementia, given the likely role of inflammation in HIV neuropathogenesis. Pentoxifylline blocks TNF-induced neurotoxicity in vitro[151,324] and, in HIV-infected patients treated with pentoxifylline for four weeks, immune activation and serum TNF-α levels significantly declined.[325,326] These agents have not yet been tested in patients with HIV dementia, and there are reasonable concerns remains that they may have intolerable side effects,[327] or may be more deleterious than beneficial.[328–330]

MMP Inhibitors

Matrix metalloproteinases are a promising therapeutic target not only for HIV dementia, but also for other neurological and systemic diseases. Many small-molecule, broad-spectrum MMP inhibitors have been designed and even been tested in humans, typically in patients with metastatic cancer. These could be tested in patients with HIV dementia as well. Minocycline is already in clinical use as an antibiotic, crosses the blood brain barrier well, and inhibits MMPs, inflammatory cytokines, and free radicals. It has demonstrated neuroprotective properties in several in vitro and in vivo models.[331] It inhibits MMP by direct effects on the active site, but also decreases MMP production and reduces MMP associated chemotaxis.[332–334] Statins also inhibit production of MMPs[335,336] and other cytokines,[337,338] and thus may have similar usefulness. Recent in vitro work suggests that MMPs may have both beneficial and deleterious effects in HIV dementia[200] and, therefore, a very clear understanding of this balance and more targeted MMP inhibition, or even augmentation, may prove to be the optimal strategy in utilizing this therapeutic option.

Monoclonal Antibodies

The use of monoclonal antibodies is another immunomodulatory technique that has been popular recently for a wide range of diseases. They could be used against numerous targets in HIV infection and HIV dementia, including viral entry receptors like CXCR4 and CCR5, leukocyte transmigration receptors such as VCAM-1 and ICAM-1, inflammatory mediators such as TNF-α and IL-1β, and even viral proteins like gp120 and Tat. As demonstrated recently when patients with multiple sclerosis were treated with natalizumab and developed progressive multifocal leukoencephalopathy,[339] the danger with monoclonal antibodies is the possibility of disrupting the beneficial effects of target

antigens, along with the deleterious effects.

Small Interfering RNA

Strong antiviral efficacy has been demonstrated with various HIV specific small interfering RNAs, suggesting great promise for this technique in preventing HIV neuropathogenesis and neuroinvasion.[340] Small interfering RNA was designed to specifically target sequences of the viral genome that are conserved in neurotropic strains isolated from brain and CSF. The RNA that targetted gp41 showed significant antiviral effect.

Neurotransmitter-Based Therapies

Memantine, an NMDA antagonist, had been shown in vitro to prevent synergistic neurotoxicity of Tat and gp120, presumably by blocking Tat and gp120 mediated glutamate excitotoxicity.[341–343] Memantine has also demonstrated a neuroprotective effect in vivo in a murine model of HIV encephalitis.[344] However, a recent randomized, multicenter, 16-week placebo-controlled study[345] of memantine in forty-five patients with HIV-associated peripheral neuropathy failed to show any trend toward clinical benefit.

Pentamidine is also an NMDA antagonist[346] and is sometimes used for pneumocystis pneumonia prophylaxis or treatment in HIV infection. As such, it may be useful for the simultaneous treatment or prevention of two different HIV complications. Several pentamidine analogs, which are even more potent glutamate antagonists, are available for study.[347]

Compounds with the ability to upregulate EAAT2, the primary glutamate transporter responsible for inactivation of synaptic glutamate, would seem to be as promising as glutamate antagonists. Gp120, in particular, increases excitoxicity by downregulating EAAT2.[125,126] Many beta-lactam antibiotics are potent stimulators of EAAT2 expression, both in vitro and in vivo.[348] In fact, ceftriaxone was protective in murine models of ischemic injury and motor neuron disease.

Targetting Tat and Gp120

The most promising of viral protein targets are Tat and gp120, due to their numerous known mechanisms of neurotoxicity. Nimodipine, a calcium channel blocker, has demonstrated efficacy in vitro in attenuating intracellular calcium fluxes caused by both Tat[349] and gp120.[350–353] A small, phase II, placebocontrolled trial,[354] involving 41 patients with HIV dementia, some of whom also had HIVrelated peripheral neuropathy, failed to show significant benefit on a composite neuropsychological test score, but underpowered to do so, and did show a favorable trend both in neurocognitive scores and in stabilization of peripheral neuropathy.

Lithium and valproate both inhibit glycogen synthase kinase 3β, through which Tat mediates some of its neurotoxic effects.[309,310] Furthermore, a recent study showed neuroprotective efficacy of valproate in vitro against gp120 induced effects on rat cortical neurons.[311] Potential benefits of valproate have also been shown in vivo in a murine model of HIV encephalitis.[311] Amiloride is a readily available diuretic, which may block the effect of gp120 on a sodium-proton exchanger, thereby reducing gp120's ability to cause glutamate-associated excitotoxicity.[122]

Although use of currently available and FDA approved agents has many obvious advantages, maximal efficacy against viral proteins is likely to be achieved only with specifically designed agents, similar to the development of agents to target reverse transcriptase or protease. Peptide T was specifically designed to block binding of gp120 to host cells, perhaps by blocking the CCR5 receptor.[355,356] Since CCR5 is the primary receptor that HIV uses to enter monocytes, which, in turn, carry the HIV from the periphery to the brain, there was great hope that peptide T would have significant benefits for HIV dementia. In vitro studies demonstrated that peptide T could prevent cell death induced by gp120 in cortical rat neurons through an effect likely mediated at the CCR5 receptor,[357] and through modulation of inflammatory cytokines.[357–360] Several small clinical trials also suggested benefit.[361–363] In larger, double-blind, placebocontrolled, phase II trials,[364,365] it showed significant improvements in several neuropsychological subset scores, especially in patients with greater baseline dementia or CD4 cell counts over 200,[365] but failed to show overall for either peripheral neuropathy[364] or HIV-associated cognitive dysfunction.[365]

Developments in the Treatment of HIV-Associated Peripheral Neuropathy

Gp120 has been strongly implicated in the pathogenesis of HIV-sensory neuropathy, so treatments that target gp120 might be beneficial for both HIV dementia and HIV neuropathy. In one study, gp120 interacted with Schwann cells via the chemokine receptor, CXCR4, leading to production of RANTES, which in turn caused dorsal root ganglion neurons to release TNF-α with subsequent neuritic degeneration and neuronal apoptosis.[366] Interestingly, erythropoietin could prevent sensory axonal degeneration and dorsal root ganglion neuronal death, apparently by blocking these gp120 effects.[367] Furthermore, erythropoietin protected cerebrocortical neurons from gp120 induced damage,[368] suggesting that gp120 induced damage to central and peripheral nervous systems may be mediated by overlapping mechanisms.

Opportunistic cns infections

Cryptococcal Meningitis

Although usually called cryptococcal meningitis, this infection is more appropriately be termed a meningoencephalitis, because the brain parenchyma is invariably involved along with the subarachnoid space. In parts of the world with the highest HIV prevalence, cryptococcal meningitis is the leading cause of community acquired meningitis, even ahead of pneumococcal and meningococcal meningitis.[369] Clinical presentation is similar to any other subacute or chronic meningitis with symptoms including headache, fever, and altered mental status, and focal neurological deficits, evolving over several weeks. Due to a high load of organism in the CSF, diagnosis is usually confirmed easily by India ink preparation of the CSF. Elevated intracranial pressure is a common cause of death, and mortality from HIV-associated cryptococcal meningitis is in the 10%–30% range,[370] even higher in developing countries.[371–373] The disease is uniformally fatal if left untreated, or treated inadequately.[374]

The causative organism, *Cryptococcus neoformans*, is a fungus found widely in the environment, particularly in waste products from pigeons and other birds, but it rarely causes clinical infection, except in immunocompromised individuals. Infection is probably acquired by inhalation of small yeast cells or spores. In immunocompetent individuals, primary pulmonary infection is usually asymptomatic and eliminated by the immue response. However, in immunocompromised individuals, and possibly dependent on virulence factors such as the organism's polysaccharide capsule, infection can become disseminated and has a preference for entering the central nervous system. In HIV-infected patients, clinical disease is associated with CD4 counts below 100 cells/pL. Cryptococci may also remain latent within pulmonary granulomas, and then cause clinical infection upon immunosupression.[375] One study suggested that the organisms may reactivate to cause infection after greater than nine years of latency.[376] Control of cryptococcal infection is strongly associated with intact cell mediated immunity and with production of Th1 cytokines, including TNF-α, IL-6, IL-12, IL-18, and IFN-γ.[377,378] Infection within the CNS is associated with a poor CSF inflammatory response.

Table 17–9 lists preferred treatment regimens for cryptococcosis. Amphotericin B is the mainstay of cryptococcal treatment. This agent binds to ergosterol in the fungal plasma membrane, increasing membrane permeability to protons, potassium, and other cations, producing reactive oxygen species, and promoting an inflammatory cytokine response.[379,380] Current guidelines for the treatment of cryptococcosis[381,382] recommend doses of 0.7 to 1 mg/kg/day.[383] There is no oral absorption of this drug, so it is administered by daily intravenous (IV) infusion and has a half-life of 24 hours. Metabolic pathways are unknown, but urine and serum levels are equivalent. Cerebrospinal fluid levels are approximately 3% of serum levels. Amphotericin has a narrow therapeutic window, because of nephrotoxicity, and kidney function must be carefully monitored during use of this drug. Amphotericin is also difficult to tolerate because it causes constutional and gastrointestinal symptoms, including chills, nausea, and vomiting. These symptoms can be attenuated by pretreatment with antiemetics and anti-inflammatories. Amphotericin is also associated with anemia and infusion site reactions. Nephrotoxicity and other adverse effects can be significantly decreased by slower rate of infusion of drug and by infusion of at least one liter per day of normal saline.[384,385] Concurrent use with other nephrotoxic drugs should be avoided. Another formulation of amphotericin, liposomal amphotericin B, allows patients to tolerate doses of up to 15 mg/kg,[386] although

whether this is any more efficacious for cryptococcal meningitis than conventional amphotericin B at 0.7 mg/kg is not known,[377,387] and the cost of the liposomal preparation is 50–100 times greater.[388].

Table 17–9 Recommended Anticryptococcal Regimens Based on Guidelines of the Infectious Diseases Society of America[381,382]
Preferred Regimens
(amphotericin B or liposomal amphotericin) + flucytosine for two weeks, then fluconazole
Alternative Regimens
(amphotericin B or liposomal amphotericin) for two weeks, then fluconazole
fluconazole
fluconazole + flucytosine for two weeks, then fluconazole



Flucytosine is typically used in combination with amphotericin. Cryptococcus contains cytosine deaminase, an enzyme that mammalian cells do not have. This enzyme converts flucytosine to 5-fluorouracil, a pyrimidine analogue that inhibits nucleic acid synthesis in the fungi. Monotherapy with flucytosine leads to drug resistance, but this problem is avoided by combination with amphotericin.[377] The combination is also more efficacious than amphotericin alone in terms of early fungicidal activity,[385] recurrence rates and CSF sterilization at two weeks.[389] The pharmacokinetics and adverse effects of flucytosine have recently been the subject of a comprehensive review.[390] The drug has a half-life of 3–4 hours, and typical dosage is 100 mg/kg/day divided into four doses. It can be used either orally or by IV infusion; bioavailability by the oral route is greater than 80%. It is eliminated primarily unchanged in the urine. This drug is water soluble and penetrates all tissues well, including the CSF, where levels are 80% of that in the serum. Adverse effects include myelosuppression and gastrointestinal symptoms, but the drug is generally well tolerated at the 100 mg/kg/ day dose. Concurrent use with other myelosuppressive agents should be avoided. Serum drug concentrations should be monitored two hours after an oral dose with goal peak level between 50 and 100 mcg/mL. Myelosuppresion is minimized if peak level is kept below 100 mcg/mL, and the dose must be adjusted for renal insufficiency, which can occur due to concurrent use of amphotericin B. Another adverse effect of particular interest to neurologists is peripheral neuropathy, possibly due to mitochondrial toxicity, but this effect is rarely clinically significant or treatment limiting.

Fluconazole is sometimes used in place of amphotericin in anticryptococcal regimens. This agent inhibits synthesis of fungal ergosterol, an important component of the fungal plasma membrane. In an early study,[391] efficacy of fluconazole monotherapy and amphotericin B monotherapy were found to be similar in terms of mortality rates, rates of clinical improvement, and rates of negative CSF culture at 10 weeks. However, amphotericin B had a significantly shorter median time to CSF sterilization. Both agents were used at lower doses than currently recommended, and neither monotherapy regimen was nearly as effective as the higher dose dual therapy regimens currently used. The combination of fluconazole and flucytosine,[392] like the combination of amphotericin and flucytosine, is more effective then any monotherapy regimen. The pharmacokinetics of fluconazole have recently been reviewed.[393] Fluconazole has a half-life of 30 hours and is therefore typically dosed on a daily basis. It can be used either orally or by IV infusion; bioavailability by the oral route is greater than 90%. It is eliminated primarily unchanged in the urine. Cerebrospinal fluid levels are greater than 50% of that in the serum. Gastrointestinal symptoms are the most common adverse effects, but are rarely treatment limiting. Transient hepatic enzyme elevation occurs in about 5%, but requires discontinuation in less than 1%. Reversible alopecia occurs in 10%–20% when doses of 400 mg/day are used with a typical time of onset about 3 months after treatment initiation.[394] Fluconazole is a cytochrome P450 inhibitor; care must be taken because it increases levels of numerous P450-metabolized drugs. However, it can be used with protease inhibitors and non-nucleoside RT inhibitors without any dose adjustments.[259]

Based on the slow initial response to fluconazole, but apparent efficacy over longer time periods, a trial[389] was conducted evaluating the efficacy of a two-week induction phase with amphotericin B with or without flucytosine, followed by an eight-week maintainence phase with either fluconazole or itraconazole. The best 10-week mortality rate thus far seen with cryptococcal meningitis was obtained at only 9.4%. Based on this study, current guidelines[381,382] indicate treatment with two weeks of amphotericin B 0.7–1 mg/kg/day plus flucytosine 100 mg/kg/day, followed by eight weeks of fluconazole 400 mg/day, followed by fluconzole 200 mg/day until immune reconstitution. Antifungal therapy should not be discontinued prior to establishment of effective antiretroviral therapy, because this increases the risk of cryptococcal recurrence both within and outside of the nervous system.

Guidelines for management of elevated intracranial pressure due to cryptococcal meningitis are based largely on anecdotal reports and expert opinion. Brain imaging is required to assess the risk of cerebral herniation due to lumbar puncture. Then, in patients with an opening pressure of greater than 25 cm water, daily lumbar punctures are recommended to achieve a closing pressure of less than 20 cm water or 50% of the opening pressure.[381] If this fails to adequately control intracranial pressure, a temporary lumbar drain may be used to remove up to 200 cc of spinal fluid per day.[395] Intraventricular shunting may also be used, but generally only in cases of obstructive hydrocephalus[396]

Cytomegalovirus (CMV)

The prevalence of CMV seropositivity is very high, both in the general population and in HIV-infected individuals.[397] In the pre-HAART era, CMV reactivation was the most common opportunistic infection in AIDS patients, at least in some studies, and caused high morbidity and mortality.[398] HAART has substantially decreased the incidence of CMV manifestations.[268] As with HIV dementia, the incidence may be declining, but the prevalence is rising as more patients live longer with HIV and CMV. Cytomegalovirus infection is usually asymptomatic in immunocompetent individuals, but, in the immunosuppressed, it can affect the gastrointestinal tract, liver, lung, retina, and nervous system. Clinical manifestations of nervous system infection include encephalitis,[399] myelitis, polyradiculitis, and neuropathy,[400–402] usually with subacute onset over weeks. These manifestations usually only occur when the CD4 count drops below 50 cells/uL. Clinical signs and symptoms are nonspecific and can represent many other opportunisitic infections or HIV itself. Diagnosis is therefore made based on a high degree of suspicion and CMV polymerase chain reaction (PCR) positivity in the CSF. The sensitivity of the PCR is greater than 80% and the specificity is greater than 90%.[403–405] Cytomegalovirus viral load can be monitored to assess therapeutic efficacy.[406] The presence of CMV retinitis is strongly associated with the presence of CMV encephalitis,[407] so the diagnosis of one should prompt strong suspicion and investigation for the other. Symptomatic neurological CMVdisease is uniformally and rapidly fatal if left untreated.[397] Cytomegalovirus viremia always precedes symptomatic CMV disease, so prevention (as opposed to treatment) of symptomatic disease is possible and preferable.[408–410] Treatment recommendations are based on survival outcomes from well-designed, randomized, double-blind trials conducted during the pre-HAART era with patients who had various CMV manifestations, but not from trials involving patients with only neurological manifestations.[397] It is therefore still unknown if any current treatment is benefical for patients with CMV-related neurological disease, and, in fact, some studies have suggested that treatments do not prolong survival in patients with CMV related encephalitis or myelitis.[411] Further, treatment of patients with non-neurological CMV disease may not prevent them from developing CMV encephalitis.[412]

Table 17–10 lists preferred treatment regimens for CMV. Ganciclovir is the mainstay of treatment for CMV disease. Ganciclovir is a synthetic analog of guanine that works as a nucleoside inhibitor for CMV replication. Current guidelines for prevention of CMV disease in high-risk patients recommend doses of 1000 mg by mouth three times daily, based on a trial demonstrating that such treatment reduces the risk of CMV disease in patients with advanced AIDS.[413] In patients with established neurological disease, treatment is often initiated with 5 mg/kg IV every 12 hours for 14–21 days.[414] Maintainence therapy is continued either with 5mg/kg IV daily[414] or with the oral prevention regimen, until the CD4 count has remained above 100 cells/uL for at least six months.[415–417] Oral maintainence regimens are associated with an earlier time to relapse (particularly for CMV retinitis), but with the benefit of avoiding inconvenience, cost, and complications of longterm IV therapy and indwelling cathethers.[418] Oral bioavailability is poor, but improved with meals, so ganciclovir should be taken with meals. Valganciclovir is sometimes used instead of ganciclovir. This is based on a randomized, open-label study of patients with CMV retinitis in which oral valganciclovir, 900 mg two times per day for three weeks followed by 900 mg daily, and intravenous ganciclovir, 5 mg/kg twice daily for three weeks followed by 5 mg/ kg daily, were equally effective in preventing progression of disease at four weeks.[419] Valganciclovir is a prodrug of ganciclovir, which is rapidly hydrolyzed to ganciclovir after administration. The profile ofvalganciclovir is therefore very similar to that of ganciclovir, except that its oral bioabsorption is much

better, on the order of 60% with food. The half-life of these drugs is approximately six hours with intravenous administration and up to 10 hours with oral administration. Ganciclovir is excreted mostly unchanged in the urine.[414,420] Cerebrospinal fluid levels are around 50% of serum levels. Myelosuppression is a significant toxicity and requires discontinuation or treatment with GCSF in greater than 20%. These drugs should not be started in patients with an absolute neutrophil count of less than 500/uL or a platelet count of less than 25,000/uL.[414] Neurological adverse effects, including headache, seizure, and confusion, are also frequent,[414] and can be difficult to distinguish from the effects of CMV encephalitis itself. Concurrent use with AZT and other myelosuppressive drugs should be avoided. Ganciclovir/valganciclovir significantly increases serum levels of didanosine.[421]

Table 17–10 Recommended Anti-CMV Regimens
Preferred Regimens
(ganciclovir or valganciclovir)
Alternative Regimens
foscarnet
foscarnet + (ganciclovir or valganciclovir)

Foscarnet is a pyrophosphate analogue that inhibits viral polymerases by interfering with exchange of pyrophosphate from deoxynucloside triphosphates during viral replication.[422] It is sometimes used in addition to or in place of ganciclovir in anti-CMV regimens. This is based on an open-label, noncomparative study,[423] in which combination therapy with foscarnet 90 mg/kg IV and ganciclovir 5 mg/kg IV, both agents twice daily for three weeks followed by both agents once daily, improved or stabilized 74% of 31 patients with CMV encephalitis or myelitis at three weeks. Most of the patients progressed or died by the end of three months, however. Furthermore, several studies have suggested that foscarnet monotherapy and ganciclovir monotherapy are equally efficacious in the treatment of CMV retinitis, and that foscarnet monotherapy is associated with increased survival.[424–426] However, because of the toxicities associated with foscarnet, and the fact that it is only available in an intravenous formulation, current guidelines recommend that use be limited to those patients with CMV infection that is resistant to ganciclovir.[397] Typical dosage is 90 mg/kg twice daily for 14–21 days, followed by maintainence with 90–120 mg/kg daily. Survival may be better with the 120 mg/kg/day maintainence dose.[427] Often, 90 mg/kg/day is used for initial maintainence, with increase to 120 mg/kg/day for maintainence after reinduction for a relapse. The half-life is approximately three hours and it is excreted mostly unchanged in the urine. Cerebrospinal fluid levels are around 50% of serum levels. The major toxicity is dose-dependent renal failure, which occurs in up to 40% of patients, usually in the second week of induction. It is usually reversible within one week of discontinuation of the drug, but requires monitoring of creatinine clearance two to three times per week during induction and every one to two weeks during maintainence. Dose must be modified depending on creatinine clearance, and the drug must be stopped if clearance drops below 0.4 mL/min/kg. Electrolytes must also be monitored twice per week during induction and once per week during maintainence, because of frequent decreases in calcium, potassium, magnesium, and phosphate levels. Seizures occur, usually related to renal failure and hypocalcemia. Adequate hydration can minimize these toxicities.[428] Concurrent use with pentamidine may cause severe hypocalcemia,[429] and use with other nephrotoxic drugs should be avoided.

Resistance to ganciclovir is frequent.[430–432] Ganciclovir therapy of under three weeks duration does not significantly increase rates of resistance, whereas therapy for 150 days or more may be associated with very high levels of resistance.[433] Ganciclovir resistant strains are not cross-resistant to foscarnet. However, frequency of resistance to foscarnet is also high at 20%–30% after 6–12 months of foscarnet treatment.[434]

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is caused by human polyomaviruses, most commonly JC virus. Like CMV and many of the herpes virus syndromes, PML occurs after reactivation of the virus in immunodeficient patients. Evidence, especially based on the occurrence of PML in multiple sclerosis patients treated with natalizumab, suggests that the reactivation occurs in B lymphocytes or the bone marrow, and the virus is then carried into the CNS from the blood, where it can cause PML, possibly due to poor cell mediated immunosurveillance.[435–439] In fact, cell-mediated immunity seems to control this virus in normal individuals,[440,441] with clinical disease occurring when cell-mediated immunity has become too suppressed to respond. JC virus primarily affects oligodendrocytes, while astrocytes may harbor nonproductive infections, and neurons seem not to be infected.[442] Pathologically, PML is marked by large distorted oligodendrocyte nuclei with intranuclear inclusion bodies surrounding areas of focal demyelination, and bizarre astrocytes within the areas of demylination, which frequently contain viral DNA, but rarely contain viral protein.[443] Clinical presentation of PML is highly variable. Onset is gradual and includes personality change, cognitive decline, hemiparesis or hemisensory deficits, visual field cuts or cortical blindness, aphasias, brainstem, and cerebellar symptoms.

It is likely that HIV proteins can interact with proteins introduced by various opportunistic viral infections to have synergistic deleterious effects. This is particularly true in PML, where the HIV Tat protein has been found in patients' JC virus-infected oligodendrocytes, and can transactivate the JC virus promoter, likely contributing to the neuropathogenesis of PML.[87,444,445]

There is no satisfactory treatment for PML, other than instituting HAART therapy and, of course, appropriate supportive measures. Progressive multifocal leukoencephalopathy generally occurs when the CD4 count drops below 200 cells/uL, providing an opportunity for recovery with immune reconstitution. Before HAART, one year survival in HIV positive patients with PML was only 10%,[446] but with HAART, it has increased to 50%.[447] However, even in survivors, remyelination does not occur in affected areas, so most are left with severe neurological morbidity.

Given the high morbidity and mortality, numerous treatments have been attempted for PML, but none with robust evidence for success. Although cytarabine (ARA-C) shows good effect against JC virus in vitro,[448] it has poor CNS penetration,[449] and a multicenter prospective trial of both intravenous and intrathecal cytarabine failed to show an additional benefit over standard antiretroviral treatment in the pre-HAART era.[450] Also, significant myelosuppression was a common adverse effect. More recently, cidofovir failed to show any additional benefit over HAART alone in a prospective, open-label, multicenter trial[451] and in several retrospective trials.[447,452,453] Interferon-α has had anecdotal success, but showed no additional benefit over HAART in a large, retrospective study.[454] Recently, many experts have started using mirtazapine in patients with PML, although there has been no clinical data to support this practice. It is based entirely on a single in vitro study[455] suggesting that the 5HT-2A serotonin receptor is an important receptor for cellular entry of JC virus, and that antagonizing this receptor prevented viral infection. Mirtazapine antagonizes and downregulates these receptors.

Toxoplasmosis

Toxoplasmic encephalitis may be the most common CNS opportunistic infection in the HAART era. The causative organism, *Toxoplamsagondii*, is an intracellular protozoan parasite found widely in domestic cats, but rarely causing clinical infection, except in immunocompromised individuals (and in the babies of woman who become infected while pregnant). Infection is usually acquired by the fecal-oral route, through ingestion of oocysts found in cat feces. Humans can also be infected by ingestion of undercooked, cyst-containing meat. As with other opportunistic infections, such as cryptococcosis, clinical toxoplasmosis in the immunocompromised is probably not due to primary infection, but rather to reactivation of latent infection.[456] Toxoplasmic encephalitis usually presents with multifocal cerebral lesions, and not as a diffuse encephalitis. Signs and symptoms, therefore, are frequently focal or multifocal, and depend largely on the anatomic location of the lesions. Nonfocal findings, including headache, fever, mental status changes, and seizures, are also common.[457,458] Manifestations usually only occur when the CD4 count drops below 100 cells/uL.[457]

Diagnosis is usually made on the basis of compatible history, exam, and imaging. Brain MRI typically demonstrates one or more ring enhancing lesions with surrounding edema and mass effect, located anywhere in the brain.[459] In this setting, empiric treatment is usually initiated, with brain biopsy only if the patient fails to respond. Biopsy is the only means of definitive diagnosis, by demonstrating typical tachyzoites in the periphery of lesions. The major alternative diagnosis in this clinical setting is primary CNS lymphoma, which is much more common with a unifocal brain lesion, suggesting that such patients may benefit from earlier biopsy.[459] Patients with high titers of

antitoxoplasma IgG are at increased risk for developing toxoplasmosis,[460] but the test is not helpful for diagnosis because of the high positivity in the general population, as well as a low but significant false negative rate.[457,458] Single-photon emission tomography and positron emission tomography, in combination with toxoplasma serologies can help differentiate toxoplasmic encephalitis from lymphoma,[461,462] although they may not be as useful in patients taking HAART.[463] Spinal fluid examination is also not helpful because it will be either normal or nonspecifically altered, with elevated protein, low glucose, and/or a mild, mononuclear pleocytosis.[458] Cerebrospinal fluid exam can, however, be useful in decreasing the likelihood of lymphoma, by demonstrating absence of malignant cells and a negative Epstein-Barr virus PCR.

As with other opportunisitic infections, the incidence of cerebral toxoplasmosis has significantly decreased in the HAART era,[464,465] while the prevalence has remained essentially stable.[466] Interestingly, both incidence and prevalence were actually already decreasing before the advent of HAART, due to increasing use of effective prophylactic regimens.[464,467,468] Morbidity and mortality has significantly decreased in HAART era,[469] but one year mortality is still as high as 23% with lack of HAART after diagnosis of toxoplasmosis negatively affecting surivival.[470] Thus, as with the other opportunistic infections, patients who develop toxoplasmosis should have effective HAART initiated as soon as possible.

Table 17–11 lists preferred treatment regimens for toxoplasmosis. The mainstay of treatment for cerebral toxoplasmosis is combination pyrimethamine and sulfadiazine. Both of these medications inhibit folate metabolism in the parasite. In patients with established neurological disease, treatment is often initiated with pyrimethamine at a loading dose of 200 mg by mouth, followed by 50–100 mg by mouth daily. Sulfadiazine is used at a dose of 1–2 g by mouth every six hours. This induction phase is continued for six weeks. Then, maintainence therapy is employed with 25–50 mg per day of oral pyrimethamine and 500–1000 mg of oral sulfadiazine every six hours, until the CD4 count has remained above 200 cells/uL for at least six months.[456] A favorable response occurs in greater than 75% of patients within two weeks of treatment initiation.[458,471] Therefore, patients who do not respond in this time period should usually receive brain biopsy to exclude lymphoma. When patients are treated in this manner for presumptive toxoplasmosis, steroids should not be used because primary CNS lymphoma often responds well, although transiently, to steroids, which can be misinterpreted as a response to antitoxoplasmosis therapy.[456]

Table 17–11 Recommended Antitoxoplasmosis Regimens
Preferred Regimens pyramethamine + sulfadiazine folinic acid + pyramethamine+sulfadiazine
Alternative Regimens clindamycin + pyramethamine clindamycin + folinic acid + pyramethamine sulfamethoxazole + trimethoprim for four to six weeks, then atovaquone

Bioavailability of both these drugs is very good. The half-life of pyrimethamine is greater than 100 hours and of sulfadiazine is about 17 hours. Pyrimethamine, sulfadiazine, and their metabolites are excreted in the urine. There is no need for dose adjustment of the pyrimethamine with renal failure, while the sulfadiazine must be adjusted. Sulfadiazine undergoes significant hepatic acetylation prior to excretion.[472] Cerebrospinal fluid levels of pyrimethamine are 12%–25% of serum levels[473] and of sulfadiazine are 40%–80% of serum levels.[474] Unfortunately, adverse reactions to these drugs, including myelosuppression from the pyrimethamine and significant rash from the sulfadiazine, occur in up to 50% of patients, and frequently require discontinuation.[458,471,475]Folinic acid (leucovorin), at a dose of 10 mg by mouth daily, should be added to this regimen because it helps minimize the hematopoeitic toxicity of the pyrimethamine. From the neurological perspective, dose-related ataxia, tremors, or even seizures can be seen. Concurrent use with AZT and other myelosuppressive drugs should be avoided, and an interaction with lorazepam can cause hepatotoxicity.

A combination of pyrimethamine and clindamycin is frequently used in patients who fail to tolerate pyramethamine/sulfadiazine. This combination is better tolerated and has similar efficacy at least initially,[476] although probably with worse long-term efficacy.[458,471] Although studies consistently show insignificant trends toward better outcomes with pyrimethamine/ sulfadiazine,[471,475] a recent meta-analysis found no significant mortality difference.[477] Induction and maintainence therapy is the same as for the pyrimethamine/sulfadiazine combination, except clindamycin is substitituted for the sulfadiazine. Clindamycin doses of 600–900 mg by mouth or intravenously are used every six hours for the six-week induction phase, followed by 300–450 mg by mouth every six hours during the maintainence phase.[456] Clindamycin interferes with protein synthesis in the parasite. Oral bioavailability is greater than 90%.[478] Central nervous system penetration is poor, but CSF levels are well above the 50% inhibitory concentration and the parasicidal concentration.[479] The half-life is approximately three hours.[480] Gastrointestinal (GI) side effects, particularly diarrhea, are common, and about 5% of patients develop *Clostridium difficile* infection, which requires discontinuation of the drug, but generally responds well to metronidazole.[481] Concurrent use of agents such as loperamide or Lomotil may increase the risk of *C. difficile* infection and other GI side effects, although this is debated and there is no definitive evidence that these agents alter the natural history of *C. difficile* infection.[482]

Current guidelines for prevention of toxoplasmosis in high risk patients recommend the use of combination trimethoprim/sulfamethoxazole (cotrimoxazole) at a dose of 160/800 mg by mouth daily, with discontinuation when the CD4 count remains above 200 cells/uL for at least three months.[456] In patients who cannot tolerate the pyrimethamine, cotrimoxazole may be used for treatment as well. Doses of 5/25 mg/kg orally or intravenously every 12 hours for four to six weeks can be used for induction, followed by atovaquone 750 mg by mouth every 6–12 hours for maintainence.[456] Regimens without pyrimethamine are felt to be substantially less effective, but evidence to support such a view is lacking. In fact, the only randomized, double-blind trial to compare cotrimoxazole with pyrimethamine/sulfadiazine found no significant differences,[483] and cotrimoxazole may be especially valuable in resource-poor settings where pyramethamine/ sulfadiazine is not available.[477]

Immune Reconstitution Inflammatory Syndrome (IRIS)

In addition to obviously treating the underling HIV, inititiation of antiretroviral therapy and subsequent immunorestoration can be one of the most effective means of treating (or preventing) opportunistic infections. However, this can be associated with an inflammatory response, as the restored immune system reacts vigorously to the presence of the opportunistic infection. Such patients will demonstrate paradoxical clinical deterioration in the setting of increasing CD4 counts and decreasing HIV viral loads and loads of opportunistic infection.[484] Immune reconstitution inflammatory syndrome can be associated with any of the opportunistic infections, but is most common with cryptococcal meningitis and pulmonary mycobacterial disease, and may occur in about 30% of patients with these conditions when started on HAART.[485] It occurs in about 20% of patients with PML when they are started on HAART.[486] Immune reconstitution inflammatory syndrome can also occur upon initiation of HAART in patients without overt opportunistic infection, probably representing presence of subclinical opportunistic infections or immune response to the HIV itself. Manifestations include fever, lymphadenopathy, and deteriorating mental status. Risk factors for developing IRIS include initiation of HAART within two months of HIV diagnosis or diagnosis of opportunistic infection, greater immunosuppression, higher load of HIV or opportunistic organisms. In patients with suspected IRIS, it is necessary to exclude drug toxicity, disease progression due to noncompliance with therapy, resistance to therapy, and inadequate therapeutic levels due to other causes such as malabsorption or drug-drug interaction.[484]

With cryptococcal infection, signs and symptoms of IRIS may include headache, elevated intracranial pressure, and pulmonary infiltrates, even in the setting of sterile CSF fungal cultures and markedly decreased cryptococcal antigen levels.[487,488]

Approximately 10% of PML cases are inflammatory in nature, as determined by enhancement on brain MRI or inflammation on biopsy. This usually happens in the setting of initiation of HAART, and is attributed to immune reconstitution.[486,489,490] Interestingly, this form of PML has a favorable prognosis, compared to typical noninflammatory PML,[491] suggesting that the inflammatory response may actually be protective against JC virus. Pathological specimens have suggested that PML associated IRIS may be due to an imbalance in lymphoctic response to the JC virus, with an excessive CD8+ cytoxic T lymphocyte response and a paucity of CD4+ regulatory T-cell response.[492] Cytarabine may be useful in patients with PML and IRIS, because the inflammation will allow the cytarabine to enter the CNS.[493] This possibility has not been tested in any clinical trials,

however. Steroids have also been advocated in patients with inflammatory forms of PML, but since these patients often improve without treatment, such immunosuppressants are probably best avoided unless the patient has significant brain edema and impending herniation.[493]

Although there have been no good studies to clearly define these characteristics, clinical presentation of IRIS can be dramatic, and morbidity and mortality, at least in the short term, are high. Unfortunately, there are no effective, specific treatments for IRIS. For prevention, it has been suggested that initiation of HAART be delayed until antigen load of known opportunisitic infection has been reduced through use of effective therapy against those opportunistic infections. However, delaying HAART will make treatment of these opportunistic infections more difficult, and will also put these patients at risk for further AIDS-related complications. Similarly, HAART can be discontinued after development of IRIS, but at the risk of AIDS progression, and with a good chance that IRIS will recur upon HAART reinitiation. Current optimal treatment is thus considered to be primarily supportive in nature, waiting for IRIS to resolve spontaneously, with other treatments, such as steroids, used only when required to abort a life-threatening event. Some experts have advocated the use of nonsteroidal anti-inflammatory drugs, but there is little data to support this practice.[484]

Conclusions

Infection by HIV causes neuronal dysfunction and loss by numerous, interacting mechanisms. Neurological complications of HIV result from effects of viral proteins, host inflammatory mediators and susceptibility factors, and opportunistic infections. Current HAART treatment is inadequate to fully control the damage that these factors cause. However, our current understanding of HIV neuropathogenesis has afforded us numerous targets for specific therapy of HIV dementia, which we are only now beginning to exploit. It is unlikely that inhibition of any specific proinflammatory factor or group of factors could provide full neuroprotection, and combination strategies are likely to be required. Similarly, specific treatments for opportunistic infections have demonstrated varying degrees of success, but still with considerable room for improvement. Our ability to optimally intervene during these processes depends on further research and understanding of the neuropathogenic mechanisms.

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Drug Intoxications

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Drug abuse is a vexing problem. Its societal costs are immense, and individual morbidity and mortality are substantial, particularly when presenting symptoms and signs are not immediately recognized and addressed. This chapter is intended to assist physicians in the recognition and management of complications associated with popular drugs of abuse. After detailing some general considerations, we discuss some of the more established illicit drugs such as heroin and cocaine. We then consider several newer recreational drugs including methylenedioxymethamphetamine, ketamine, and gamma-hydroxybutyrate.

General Considerations

Recognizing and treating complications of recreational drug use can be difficult for a number of reasons. First, in today's drug scene, polydrug use is the rule rather than the exception, requiring that treating physicians be alert for potential drug interactions and knowledgeable of the nature and duration of combined drug effects. Second, the clinical presentation is often less than straightforward, as the history is sometimes deliberately concealed. Third, the identity and purity of the drug ingested is generally unknown, and results of drug screens are not immediately available. Fourth, physical dependence and withdrawal may complicate the clinical picture, and require that treatment be prolonged beyond the period of drug exposure. Fifth, tardive drug effects are possible, making it difficult for both the patient and the physician to link the presenting problem with prior drug ingestion. Finally, management approaches for one complication sometimes conflict with those of another. For instance, urine alkalinization and vigorous hydration are indicated for rhabdomyolysis after amphetamine intoxication. Yet, alkalinizing the urine will slow amphetamine clearance. In such situations, prioritization of management strategies is essential, as is a full understanding of relevant pathophysiologic mechanisms and the pharmacology and toxicology of the offending drug(s), discussed in subsequent sections.

Initial Measures

In light of the issues previously discussed, successful management of suspected acute drug intoxication calls for a systematic approach that begins with a series of early measures. These include obtaining a detailed history, recognizing that it is likely to be incomplete, and bearing in mind that poly-drug use is common. Vital signs and blood oxygenation should be determined and monitored frequently until the patient is stable. A complete blood count, chemistry panel, urinalysis and electrocardiogram should be obtained. It is also a good idea to collect an extra blood sample for any subsequent studies that may be needed. Urine and blood drug screens should be ordered, even though results will not be immediately available. Urine osmolality, electrolytes, and creatine kinase (CK) should be checked. Other routine measures include administration of glucose, thiamine, and naloxone to the patient with altered mental status, along with a head computed tomographic (CT) or magnetic resonance imaging (MRI) study. If there is any indication of infection, a lumbar puncture is in order. Activated charcoal to promote emesis and gastric lavage should also be considered, if recent oral drug ingestion is suspected. Finally, vigilance for emerging toxicities is critical. Having taken these initial no harm measures, mechanisms and salient features of particular drug intoxications need to be considered.

Heroin

Heroin and other opiate drugs exert their effects principally through opiate receptors, of which there are three types, mu (μ), delta (δ), and kappa (κ), all belonging to the family of G protein-coupled receptors.[1] The hallmarks of acute opiate intoxication are pupillary constriction, respiratory depression, and stupor/ coma. Although small, constricted pupils are characteristic of opiate intoxication, their absence does not exclude the diagnosis, because severe hypoxia (secondary to respiratory depression) can result in pupillary dilatation.

Respiratory depression is the major concern in heroin overdose. If present, immediate manual or mechanical ventilation is in order. Respiratory depression secondary to opiate intoxication can be readily reversed with the opiate antagonist naloxone (Narcan). Narcan can be administered either intravenously or intramuscularly, at an initial dose of 0.4 mg. A response should be evident within one or two minutes. If not, additional doses of 0.4 mg should be given. Because the duration of action of opiates varies and the plasma half-life of naloxone (Narcan) is relatively short (approximately one hour after intravenous administration), repeat doses may be necessary. For prolonged opiate antagonism, consider either a continuous intravenous infusion of naloxone starting at an infusion rate of 0.2 to 0.4 mg/hour. Longer acting opiate antagonists are also available (e.g., Nalmefene (Revex), which has a plasma half-life of approximately 11 hours).[2]

Respiratory depression, leading to cerebral hypoxia, is responsible for the major neurological complications of heroin overdose. These include seizures,[3] extrapyramidal syndromes secondary to basal ganglia injury,[4–6] cerebral infarction,[7–9] and acute or delayed post hypoxic leukoencephalopathy.[10–13] In addition to hypoxia, other possible mechanisms by which opiates may produce cerebral infarction have been invoked, and include vasculitis, vasospasm, and/or thromboembolic events.[14–16] Rarely, stroke after heroin overdose may be related to direct vascular compression compromising blood flow to the brain of an obtunded individual resting in an awkward position.[17] Management of these complications of heroin intoxication parallels the routine management of similar conditions in comparably aged drug-free individuals.

Heroin abuse can also produce neurologic complications indirectly, by means of infection, invariably secondary to nonsterile intravenous drug use. Such complications include meningitis, cerebral abscess, and, in individuals with endocarditis, septic embolic infarcts.[16] Treatment in these cases should be directed at the offending pathogen. Neurologic disturbances arising from human immunodeficiency virus (HIV) infection, also often acquired through intravenous drug use, are well chronicled and include HIV-related dementia and acute meningoencephalitis. In such patients who have no other identifiable cause of neurologic illness, measurement of cerebrospinal fluid (CSF) HIV viral load and treatment with central nervous system-penetrating highly active antiretroviral therapy (HAART) should be considered.[18] A painful sensory neuropathy responsive to treatment with topical capsaicin has also been described in HIV-infected individuals.[19]

A relatively uncommon neurological complication of heroin abuse is myelopathy,[20] typically occurring at cervical or thoracic levels. Like many of the other neurologic complications of heroin abuse, myelopathy is suspected to be secondary to hypoxic-ischemic insult. A progressive ventral pontine syndrome following heroin abuse has also been described,[21] as has a unique toxic spongiform leukoencepha lopathy associated with inhalation of preheated heroin (chasing the dragon).[22,23]

Along with brain and spinal cord insults, peripheral mononeuropathies are observed in heroin abusers. These are generally attributable to prolonged nerve compression, or to direct trauma from injection.[24] Brachial and lumbosacral plexopathies can also develop in the setting of heroin abuse. Such plexopathies may be related to local infection, rhabdomyolysis, and/or autoimmune mechanisms.[25]

Physical dependence generally develops with prolonged heroin abuse. It can be treated in several ways. Perhaps the most common involves the use of methadone (Dolophine), an orally active opiate agonist with a long duration of action. Methadone is given in daily doses ranging from 20 mg up to 100 mg. Another orally active opiate is buprenorphine (Sobutex). It is a partial opiate agonist and is given sublingually at an initial dose of 4 mg. The dose of buprenorphine can be gradually increased up to 32 mg daily without major side effects. In addition to opiate agonists, opiate antagonists such as naltrexone (Trexan) have been used to treat opiate dependent individuals seeking to avoid relapse. However, use of antagonists must be limited to detoxified addicts, because opiate antagonists can precipitate withdrawal in an opiate-dependent individual. Naltrexone is well absorbed after oral administration, not addictive and extremely effective in blocking the reinforcing effects of a wide range of opiate agonists. Yet another approach for treating heroin dependence involves gradual reduction of the opiate dose, with the ultimate goal of complete abstinence. This is often accomplished within the confines of a treatment facility. In such venues, clonidine (Catapress) at a dose of 0.2 mg given orally every four to six hours is often used to suppress symptoms of opiate withdrawal. The dose of clonidine can be increased up to 1.2 mg/day, given in divided doses. A series of rapid and ultra-rapid detoxification procedures are also evolving.[26]

Cocaine

Cocaine acts primarily by blocking the reuptake inactivation of dopamine (DA) and norepinephrine (NE), both in the brain and in the periphery.[27] Increased DA and NE in the synaptic cleft results in increased catecholaminergic neurotransmission, which in turn results in increased alertness, elevated mood, higher blood pressure and heart rate, mild hyperthermia, and reduced appetite and thirst. Signs of recent cocaine ingestion include dilated pupils, tachycardia and hyperactivity. Cocaine is often abused in conjunction with heroin (speedball).

Cocaine abuse is associated with a number of potential complications, most of which are referable to excessive stimulation of the sympathetic and central nervous systems. Such complications include hypertension, hyperpyrexia, rhabdomyolysis, cardiac arrhythmias, and sudden death.[28–31] Occasionally, these occur even after modest doses of cocaine in individuals without any predisposing factor.[31]

Common neurological complications of cocaine abuse are seizures and strokes.[3,32–36] The mechanisms by which cocaine causes stroke are complex and may include increased blood pressure, vasospasm, and/or platelet aggregation with thrombus formation.[37–41] Direct vascular injury by cocaine has also been reported.[42–44] Individuals with other risk factors for stroke (e.g., hypertension, tobacco use, hyperlipidemia) are thought to be particularly vulnerable to cerebrovascular complications of cocaine. Cocaine abuse can also cause or exacerbate movement disorders,[45–47] and induce paranoia, delirium, and psychotic states.[48,49]

Treatment of acute cocaine intoxication depends on the particular complication. Repeated seizures are best treated with intravenous diazepam, usually after intubation.[50] Malignant hypertension can be treated with standard doses of a calcium channel blocker, intravenous phentolamine or nitroglycerin. Beta blockers are generally avoided because their use results in unopposed alpha-stimulation leading to vasoconstriction.[51] Sodium bicarbonate is indicated in the setting of acute acidosis. For cocaine-related strokes, thrombolysis is not routinely indicated because it does not overcome vasospasm and can increase the risk of intracranial hemorrhage in a hypertensive patient.[31] Antiplatelet agents that prevent further thrombus formation are appropriate. Agitation is best controlled with a benzodiazepine (e.g., diazepam).

Cocaine dependence remains a therapeutic challenge.[52] Various pharmacological agents have been tried including DA uptake inhibitors (bupropion, methylphenidate), DA receptor blockers (risperidone), monoamine oxidase (MAO) inhibitors (selegiline), and GABAergic drugs (gabapentin, topiramate).[53,54] As yet, there is no agent with clear-cut efficacy for the treatment of cocaine dependence.

Methamphetamine

Methamphetamine (speed, crank) produces psychomotor stimulant effects principally by releasing DA and NE from dopaminergic and noradrenergic nerve endings.[55] Methamphetamine also blocks the reuptake inactivation of catecholamines (DA and NE), but this action is not as prominent as the releasing action. Increased catecholaminergic neurotransmission after methamphetamine leads to elevated blood pressure, tachycardia, increased temperature, mydriasis, anorexia, euphoria, and excitement. After high doses, anxiety, hallucinations and delusions may occur.[56] High doses can also produce malignant hyperthermia, hypertensive crises, seizures, cardiac arrhythmias, and cardiac arrest. Effects of methamphetamine last 6–12 hours, with some residual effects still apparent 12 hours after ingestion. A binge pattern of methamphetamine use is not uncommon and is characterized by repeated dosing over several days. Poor personal hygiene, weight loss, and erratic behavior may serve as clinical clues of methamphetamine abuse and dependence.

Neurologic complications of methamphetamine intoxication include intracranial hemorrhage,[57–59] ischemic stroke,[60–61] possible vasculitis,[62–64] seizures,[3,65] choreiform movement disorder,[66,67] headache,[68] hyperpyrexia and malignant hypertension.[68,69] Psychiatric complications usually take the form of anxiety, agitation, and aggressive behavior.[56,68] More severe acute mental status changes may include paranoia, delirium, and psychosis.[65,68] In the setting of acute methamphetamine intoxication, severe medical complications such as rhabdomyolysis and disseminated intravascular coagulation (DIC) may occur.[67,70,71]

Treatment of methamphetamine intoxication is largely supportive, and tailored to the signs and symptoms of the individual patient. Acute methamphetamine intoxication is often self-limiting, usually requiring only routine supportive care and observation. Acidification of the urine with ammonium chloride can be used to promote renal excretion of methamphetamine, unless there is a relative contraindication such as rhabdomyolysis (which benefits from alkalinization to prevent myoglobin breakdown to toxic compounds within the kidney). Blood pressure should be monitored closely, as hypertensive crisis may develop. As with cocaine intoxication, calcium channel blockers, intravenous phentolamine or nitroglycerin can be used to lower blood pressure. Temperature should also be closely monitored for signs of emerging malignant hyperthermia. When core temperatures exceed 39°C, ice baths, cooling blankets, and fans should be used to lower temperature. Agitation, anxiety and combativeness are best treated initially with benzodiazepines. If psychosis and agitation persists, an antipsychotic agent can be employed, recognizing that side effects of antipsychotics can complicate the clinical picture. Antipsychotics may also lower the seizure threshold. Intravenous diazepam is the treatment of choice for repeated seizures, after the patient is intubated to guard for potential apnea or laryngospasm.

Abrupt cessation of methamphetamine use results in a withdrawal syndrome characterized by depressed mood.[72] Some authors have noted psychotic symptoms that persist for months or years in some individuals.[73–75] As yet, there are no effective pharmacological treatments for methamphetamine abuse and dependence. Multipronged approaches employing a variety of cognitive, behavioral, and pharmacologic methods offer the most promise.

A growing body of evidence indicates that recreational abuse of methamphetamine is associated with damage to central dopaminergic and serotonergic neurons.[76–78] Functional consequences of methamphetamine-induced neurotoxicity remain to be delineated. Cognitive changes including deficits in learning, selective attention, delayed recall, processing speed, working memory and verbal memory have been reported in abstinent methamphetamine abusers.[79] Whether these are related to neurotoxic effects of methamphetamine remains to be determined.

Mdma

Methylenedioxymethamphetamine (MDMA, ecstasy) exerts its effects primarily by releasing serotonin (5-HT), DA, and NE, and, possibly, by also directly stimulating postsynaptic 5-HT receptors.[80] Use of MDMA is particularly common in clubs and large dance parties (raves). A noteworthy feature of MDMA is that its metabolism is nonlinear, such that plasma levels of the drug rise faster than would be predicted by increases in dose.[81,82] Consequently, higher or closely spaced doses, such as those often used in recreational settings, produce disproportionate rises in plasma MDMA concentrations, which in turn produce more pronounced effects.

Recent MDMA use is suggested by dilated pupils, nystagmus, increased heart rate and blood pressure, and jaw clenching.[83] Potential acute untoward effects of MDMA include anxiety, cardiac dysrhythmia, myocardial ischemia, hypertension, and seizures.[84] These toxicities sometimes develop even after typical single doses. Other complications reported after the use of MDMA are strokes (both ischemic and hemorrhagic),[85,86] intracerebral, subdural or subarachnoid hemorrhage,[87–89] cerebral venous sinus thrombosis,[90] cerebral edema and coma, sometimes resulting in death.[91,92] Treatment of these complications should be the same as that for their idiopathic counterparts.

Methylenedioxymethamphetamine can also induce panic disorder,[93–95] psychosis and major depressive disorder.[96–98] Most often these problems develop shortly after MDMA exposure and resolve after the drug is discontinued.

Occasionally, however, these problems prove to be long-lasting.[99,100] The role of a preexisting condition in such instances is unclear.

In addition to these complications, many of which appear related to overstimulation of the central and sympathetic nervous systems, there are four other potentially severe complications of MDMA use that warrant attention. These are: (1) malignant hyperthermia; (2) hyponatremia; (3) CK elevation; and (4) hepatotoxicity. Each of these is considered here.

Malignant Hyperthermia

This complication is most likely to develop when MDMA is used in a warm environment. It is a serious complication that can result in rhabdomyolysis, disseminated intravascular coagulation, hepatic and renal insufficiency, and, if not adequately treated, death.[101] Methylenedioxymethamphetamine-related malignant hyperthermia should be suspected in any otherwise healthy young adult who presents with an elevated temperature, a change in mental status and other signs of MDMA ingestion (e.g., nystagmus). Treatment parallels the treatment of other causes of heat stroke. In particular, whole body cooling, support of organ system function and careful attention to fluid and electrolyte balance are essential.[102] Paralysis and intubation may be necessary to reduce muscular thermogenesis. Some authors recommend use of dantrolene when core temperature exceeds 39°C.[103] For agitation, benzodiazepines should be used. Antipsychotics are best avoided because they may cloud the clinical picture by introducing the theoretical possibility of neuroleptic malignant syndrome as the case evolves. Urine acidification, to increase MDMA clearance, is not recommended because of possible coincident CK elevation and concern that myoglobin precipitation will compromise renal function.

Hyponatremia

When pronounced, hyponatremia is another serious complication of MDMA use. It can lead to seizures, cerebral edema, and death.[104] Hyponatremia is thought to develop from a combination of factors including antidiuretic hormone (ADH) release by MDMA[105] and excessive water consumption to ward off dehydration. Presenting symptoms may include nausea, vomiting, headache, and muscle cramps. In such cases, prompt assessment of volume status is critical and should include determination of serum and urine osmolality, along with urine electrolytes to assess fractional excretion of sodium. In the absence of other complications or dehydration, treatment of symptomatic hyponatremia after MDMA calls for fluid restriction, and, if necessary, cautious infusion of normal or hypertonic saline.[104] Mannitol and/or a diuretic are appropriate if cerebral edema is present.

CK Elevation

Striking increases in CK levels are occasionally seen in the wake of MDMA ingestion, sometimes in the absence of rhabdomyolysis or renal failure.[106,107] Inspection of the urine in such cases shows it to be dark, and urinalysis reveals proteinuria without hematuria. Treatment includes vigorous hydration, with careful monitoring of volume status and renal function. Electrolytes should also be monitored closely for potential hyperkalemia and hyponatremia. Management of coincident CK elevation and hyponatremia is challenging because volume expansion to promote diuresis can aggravate hyponatremia. For volume-depleted patients, careful hydration with normal saline is indicated. For patients with normal or expanded intravascular volumes, hypertonic saline can be used Alkalization of the urine should be avoided because it decreases MDMA elimination.

Hepatotoxicity

Hepatic insufficiency may develop after MDMA ingestion. It may be mild or severe.[84,108] The pathogenesis is unclear but some cases appear to be related to malignant hyperthermia. Others may result from a direct hepatotoxic effect of MDMA. The clinical presentation varies, with some patients presenting in acute crisis and others presenting with hepatotoxicity after an indolent course. Depending on the presentation, treatment has varied from nutritional support and careful longitudinal assessment of liver function, to liver biopsy and transplant.

In addition to these described complications, MDMA has been reported to produce persistent cognitive deficits in individuals without overt psychiatric diagnoses.[109,110] These deficits appear to be unrelated to poly-drug use (including marijuana), and specifically related to MDMA. The most consistently reported cognitive deficit in MDMA users has been in short term and/or working verbal memory, although other cognitive impairments have also been reported.[111–113] Because MDMA-related cognitive deficits are subtle, formal psychometric testing is needed for their detection.

Similar to methamphetamine, MDMA has been shown to produce toxic effects on brain monoamine-containing neurons.[80] In most experimental animals (including nonhuman primates), the toxic effect of MDMA is selective for brain 5-HT neurons.[114] In mice, the damage is selective for brain DA neurons. In humans, the neurotoxic effect of MDMA appears restricted to brain 5-HT neurons.[115] It is unknown whether cognitive and other lasting sequella of MDMA use are related to prior destruction of serotonergic axons and axon terminals.

Ketamine

Ketamine (special K) is an antagonist of glutamatergic N-methyl-D-aspartate (NMDA) type receptors.[116] It also blocks the DA transporter.[117] Ketamine is often referred to as a dissociative anesthetic, and is one of a group of drugs that also includes phencyclidine (PCP) is subject to abuse. In addition to its anesthetic effects, ketamine produces a mixture of psychedelic, stimulant and depressant effects.[116,118,119] Effects of ketamine on mnemonic function have received considerable attention.[120] Recently, the possibility that ketamine may replicate positive, negative and cognitive symptoms of schizophrenia has been discussed.[121]

Over the last decade, ketamine abuse has been on the rise, particularly in clubs and large dance parties, where combined use of MDMA and ketamine has been noted. Ketamine is available as a powder or a liquid. After ingestion, its effects last about an hour. Repeated dosing is not uncommon. Acute effects of ketamine include increased heart rate and blood pressure, impaired memory function, and visual alterations.[116,118,122] Dissociative or dream-like (out of body) experiences after ketamine have received much attention.

Presenting features of ketamine intoxication may include anxiety, tachycardia, agitation, and altered mental status.[123,124] Half of patients presenting to an emergency department had no complaint.[125] Respiratory depression is a concern. As high doses of ketamine can induce vomiting, aspiration precautions should be taken in the patient who is unable to protect his/her airway. Body injury secondary to failure to respond to painful stimuli (due to ketamine's anesthetic effect) can occur.

Supportive care is the mainstay of ketamine intoxication. Severe anxiety, agitation and/or hallucinations can be controlled by placing the patient in a quiet environment and through the use of a sedative (benzodiazepine or high potency antipsychotic). Rhabdomyolysis, typically secondary to agitation and combativeness, requires vigorous hydration, bearing in mind that concomitant complications due to other drugs (e.g., MDMA-induced hyponatremia) are possible in individuals who engage in polydrug use. In such cases, prioritization of intervention measures is essential (see the MDMA section). Most ketamine intoxications resolve within hours.

Like MDMA, ketamine has well documented neurotoxic potential. In particular, ketamine and other drugs that block NMDA receptors have been shown to destroy neurons in several corticolimbic regions of the adult rat brain.[126,127] Whether such neurotoxic effects occur in humans is not known, although a recent postmortem study revealed neuropatho logical findings consistent with neurotoxicity after continuous intrathecal administration of ketamine.[128]

Gammahydroxybutyrate (Ghb) And Its Analogs

Gammahydroxybutyrate, an analog of the inhibitory neurotransmitter gamma amino butyric acid (GABA), is found endogenously in the brain and CSF.[129] Gammahydroxybutyrate activates $GABA_B$ receptors, which are widely distributed throughout the brain, and generally lead to postsynaptic hyperpolarization and depression of neurotransmitter release.[130] There is some evidence that there are GHB receptors in the brain,[131] although the nature of these receptors is poorly understood. GHB is known to influence a number of non-GABAergic neuronal systems, including the dopaminergic, serotonergic and cholinergic systems, as well as endogenous opioid and neurosteroid systems.[129] It also leads to increases in the release of growth hormone, hence its use by bodybuilders.

Gammahydroxybutyrate and its precursors, gammabutyrolactone (GBL) and 1,4-butanediol (BD), are among the drugs that are used recreationally in a club setting.[132–134] In addition to recreational drug users, other populations that are known to use GHB and its precursors include bodybuilders and athletes, who use these drugs for their anabolic and energy-promoting properties. The FDA recently approved GHB for the treatment of narcolepsy.

Effects of GHB, GBL, and BD occur within 15 to 30 minutes after ingestion and can last up to six hours.[132] Adverse effects of these drugs are invariably secondary to overdose. Signs and symptoms of overdose can include CNS depressant effects of somnolence, obtundation, bradycardia, stupor and coma, as well as somewhat nonspecific symptoms of vomiting, disorientation, and confusion.[132–135] Some GHB overdose patients present with paradoxical agitation and excitement.[136] The most serious concern following GHB overdose is respiratory depression or arrest, which can lead to death. Serious complications of GHB and related drugs are more likely to occur when they are ingested along with other CNS depressant drugs, such as alcohol. Because GHB is not detected in routine drug screens, it is crucial that treating physicians are aware of the myriad signs of GHB toxicity and obtain careful histories, when available.

There are no specific treatments for GHB overdose and, as such, emergency treatment is primarily symptomatic and supportive. Gastric lavage is not useful because GHB is rapidly absorbed from the gastrointestinal tract. Because of the risk for respiratory arrest, in known cases of GHB intoxication, endotracheal intubation is indicated to protect the airway and, if necessary, to provide ventilatory support. Because patients can awaken abruptly from GHB-induced coma in an agitated or combative state, postintubation sedation with a short-acting benzodiazepine is also suggested. Respiratory and CNS depression secondary to GHB typically resolve in two to six hours.

In addition to adverse events associated with acute GHB overdose or intoxication, individuals who use GHB and its analogs chronically are known to develop tolerance and physical dependence. Abrupt cessation of GHB in such individuals leads to a withdrawal syndrome.[137] This syndrome can develop quite rapidly and persist for days to weeks. It is initially characterized by symptoms of CNS excitation such as tremulousness, anxiety, tachycardia, diaphoresis and insomnia and can rapidly progress to profound disorientation, hallucinations and psychosis. In chronic GHB users who have been using large doses of the drug on a regular basis, high doses of a benzodiazepine may be necessary to manage the symptoms of acute GHB withdrawal, and should be followed by a gradual benzodiazepine taper. Barbiturates and chloral hydrate have also been used in cases refractory to benzodiazepines. For symptoms of severe psychosis, the use of a newer antipsychotic agent is appropriate.

Conclusion

Recognizing complications of drug abuse can be difficult. Complete histories are seldom available, patients themselves may not know the true identity of the drug preparation they ingested, and tardive or delayed toxicities are possible. Treatment can also be challenging, as it requires not only thorough understanding of relevant pathophysiologic mechanisms but also detailed awareness of the pharmacology and toxicology of the drug(s) in question. These challenges notwithstanding, many drug complications can be successfully managed by using a systematic approach that begins with a series of early no harm measures, proceeds with vigilance for combined drug effects and emerging toxicities, and effectively prioritizes competing management strategies when these arise.

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